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Commentary

Functions and transcriptional regulation of adult human hepatic UDP-glucuronosyl-transferases (UGTs): Mechanisms responsible for interindividual variation of UGT levels

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ABSTRACT

Ten out of 19 UDP-glucuronosyltransferases (UGTs) are substantially expressed in adult human liver (>1% of total UGTs); 5 UGT1 isoforms (UGT1A1, 1A3, 1A4, 1A6 and 1A9) and 5 UGT2 family members (UGT2B4, 2B7, 2B10, 2B15 and 2B17) (Izukawa et al. [11]). Surprisingly, UGT2B4 and UGT2B10 mRNA were found to be abundant in human liver suggesting an underestimated role of the liver in detoxification of their major substrates, bile acids and eicosanoids. Among factors responsible for high interindividual variation of hepatic UGT levels (genetic diversity including polymorphisms and splice variants, regulation by liver-enriched transcription factors such as HNF1 and HNF4, and ligand-activated transcription factors) nuclear receptors (PXR, CAR, PPARα, etc.), and the Ah receptor are discussed. Unraveling the mechanisms responsible for interindividual variation of UGT expression will be beneficial for drug therapy but still remains a major challenge.

1. Introduction

UGTs are central Phase II enzymes of drug metabolism. They evolved as two families in mammals; 19 human enzymes are known to date exhibiting significant conjugating activity towards drugs and endobiotics. The UGT1 locus is located on chromosome 2q37 and consists of multiple first exons and shared exons 2–5. The UGT2 family is located on chromosome 4q13 and includes three members of the UGT2A subfamily and seven functional members of the UGT2B subfamily. Each UGT2 gene comprises six exons that are not shared between family members, with the exception of UGT2A1 and 2A2 [1]. UGTs are mainly expressed in liver. However, some UGTs (UGT1A7, 1A8 and 1A10) are only expressed in the gastrointestinal tract, and UGT2A1 in nasal tissue [2]. UGTs are part of an evolutionary-conserved detoxification system, also termed chemical defensome [3], which serves to prevent accumulation of lipid-soluble compounds in the organism: Phase I mainly includes CYP-mediated oxidation whereas Phase II consists of conjugating enzymes including glutathione S-transferases (GSTs), sulfotransferases (SULTs) and UGTs. Accumulating evidence suggests that the drug- or xenobiotic-metabolizing enzyme system is also involved in homeostasis of endogenous signaling molecules [4]. In order to understand hepatic drug glucuronidation it is important to know the level of liver-expressed UGTs and to understand the relationship between hepatic enzyme levels and clearance of drugs mainly eliminated by glucuronidation [2,5,6]. Due to difficulties to generate selective antibodies against all UGTs, expression levels of UGT mRNAs in adult human liver have been quantified in several laboratories [7–11], including a liver bank of 54 individuals [8]. Recently, 10 UGTs were found to be substantially expressed in human liver (>1% of total UGTs; Table 1): 5 UGT1 isoforms (UGT1A1, 1A3, 1A4, 1A6 and 1A9) and 5 UGT2 family members (2B4, 2B7, 2B10, 2B15 and 2B17) exhibiting large interindividual variation of expression [11]. Unexpectedly, UGT2B4 and UGT2B10 expression was highest in liver. In contrast, UGT2B7 was suggested to be the major hepatic enzyme based on the number of drugs mostly metabolized by glucuronidation [12]. High expression levels of UGT2B4 and 2B10 were supported by previous studies [7–10]. Although hepatic UGT protein levels and activities are required to understand interindividual variation of drug glucuronidation [8], hepatic UGT mRNA levels are particularly suitable to discuss the role of transcriptional regulation.

The present commentary briefly overviews our current knowledge about functions of the 10 major UGTs expressed in adult human liver. Extrahepatic UGTs are not in the scope of the present discussion. Among mechanisms responsible for the large interindividual variation of hepatic UGT levels (genetic diversity

Abbreviations: AhR, Ah receptor; CAR, constitutive androstane receptor; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; UGT, UDP-glucuronosyltransferase.

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Table 1
Selected endobiotic and drug substrates of 10 human hepatic UDP-glucuronosyltransferases (UGTs) [11]. Percent means of expressed UGTs are listed in parentheses. Regioselective glucuronidation is indicated. Stars list probe substrates, i.e., substrates selectively glucuronidated by a single UGT [13].

UGT (% of total [11])	Endobiotic substrates	Drug substrates
1A1 (11.3)	Bilirubin*, estradiol (3-OH) Eicosanoids Thyroxin	Irinotecan/SN38 Paracetamol
1A3 (1.4)	Estrogens, Bile acids (24-OH) Eicosanoids	Cyproheptadine
1A4 (5.5)	Estrogens Eicosanoids	Nicotine, trifluoperazine* Imipramine, lamotrigine
1A6 (6.8)	Serotonin*	Paracetamol
1A9 (5.1)	Estrogens Eicosanoids	Propofol*, mycophenolate, paracetamol
2B4 (34.5)	Bile acids (6-OH) Androstane-3,17-diol Arachidonic acid	Codeine Fibrates
2B7 (5.1)	Bile acids (3-OH), estradiol (17-OH) Progesterone Mineralocorticoids, glucocorticoids Eicosanoids Retinoids	Morphin (6-OH)*, zidovudine* Mycophenolate
2B10 (19.6)	Eicosanoids	Nicotine
2B15 (8.0)	Testosterone (17-OH)	S-Oxazepam* Paracetamol
2B17 (2.8)	Dihydrotestosterone (17-OH) Testosterone	

including polymorphisms and splice variants, tissue-specific constitutive and ligand-activated transcription factors) nuclear receptors (PXR, CAR, PPAR, etc) and the Ah receptor are discussed. Contributions of these receptors to interindividual variation of UGT expression are emphasized, in particular high expression of UGT2B4, UGT2B10 and their putative role in bile acid and eicosanoid homeostasis.

2. Overview on functions of human hepatic UGTs

Functions of UGTs are just beginning to be understood [2,5,6]. Recent evidence substantiates that UGTs are involved in conjugation of important endobiotic signaling molecules including bilirubin, steroid hormones, bile acids and eicosanoids, and of a plethora of xenobiotic phytochemicals and marketed drugs. Typical endo- and xenobiotic substrates of the 10 major hepatic UGTs are listed in Table 1. UGTs are known to possess distinct, albeit overlapping substrate selectivity towards endobiotics and drugs. UGT enzyme activity has been investigated using probe substrates, i.e., substrates conjugated by a single UGT [8,13], indicated by stars in Table 1.

2.1. Endobiotic homeostasis and detoxification by UGTs

2.1.1. UGT1A1

Is the only enzyme responsible for elimination of the heme metabolite bilirubin [2]. A significant amount of bilirubin is produced every day (250–400 mg in adult humans) primarily from hemoglobin degradation in spleen. Bilirubin is known to be neurotoxic, particularly in the newborn. Lack of functional UGT1A1 in Crigler–Najjar syndrome is fatal. Hence, the level of bilirubin-conjugating UGT1A1 has to be strictly controlled. On the other hand, bilirubin is recognized as a potent antioxidant [14,15]. Moderately increased serum bilirubin in individuals with Gilbert's syndrome has been demonstrated to be responsible for decreased risk of cardiovascular disease [16]. In addition, UGT1A1 is the major enzyme conjugating estradiol and 2-OH-catecholestrogens to 3-O-glucuronides, in contrast to UGT2B7 which conjugates estradiol and toxic 4-OH-catecholestrogens at 17-OH [17]. UGT1A1 (together with UGT1A3, 1A9, 2B4, 2B7 and 2B10) also conjugates polyunsaturated fatty acids (PUFAs) such as linoleic and arachidonic acid and their metabolites including a variety of eicosanoids [18,19], discussed in Section 4.1. The enzyme is also involved in the metabolism of many drugs including the chemotherapeutic irinotecan and its active metabolite SN38.

2.1.2. UGT1A3

(In concert with other UGTs, CYPs and SULT2A1) contributes to bile acid homeostasis in cholestasis, as discussed in Section 4.4. Estrogens [17] and eicosanoids [18] are also substrates of UGT1A3. Like UGT1A4, UGT1A3 is involved in N-glucuronidation of drugs.

2.1.3. UGT1A4

Is known to catalyse N-glucuronidation of many drugs including antidepressants (imipramine, amitriptyline, trifluperazine and the antiepileptic lamotrigine [2], and nicotine [9]). However, early evidence suggested a second enzyme forming N-glucuronides with higher affinity [20]. Recently, this enzyme was identified as UGT2B10 [9].

2.1.4. UGT1A6

Conjugates a number of planar phenols such as the neurotransmitter serotonin, suggested as probe substrate [13]. UGT1A6 conjugates paracetamol with high affinity together with UGT1A1, 1A9 and 2B15 [21,22]. It is also involved in detoxification of N-OH-2-naphthylamine, the reactive intermediate of the known bladder carcinogen, 2-naphthylamine [23].

2.1.5. UGT1A9

Is known to conjugate bulky phenols including drugs such as paracetamol and propofol, the latter suggested as probe substrate [12,13]. Endobiotic substrates include estrogens [17] and eicosanoids [18,19], discussed in Section 4.1.

2.1.6. UGT2B4

Is highly expressed in human liver [7,11]. It is important in detoxifying eicosanoids [18,19], and bile acids at 6-OH, for example hyocholic acid and hyodeoxycholic acid (Fig. 1), discussed in Section 4.4 [24–26].

2.1.7. UGT2B7

Represents a major drug-metabolizing UGT, responsible, e.g., for morphine glucuronidation [12,13]. Zidovudine (azidothymidine) has been suggested as probe substrate [13]. Elegant studies demonstrated that UGT2B7 is also the major enzyme responsible for glucuronidation of a variety of steroid hormones (estradiol at 17-OH) and 4-OH-catecholestrogens [17,27], 6- and 21-hydroxyprogesterone [28], androsterone and androstanediol [29], glucocorticoids and mineralocorticoids [27,30], retinoids [31], eicosanoids [18,19] and bile acids [24–26], discussed in Section 4.4.

Belangers's group recently summarized the role of UGTs in androgen signaling based on free and conjugated androgen serum levels [29]. Androgens are formed by both the testis and adrenals.

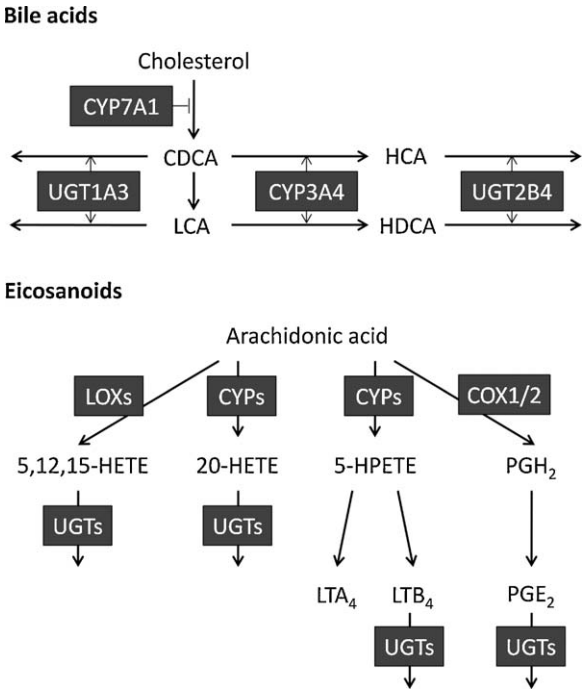

Fig. 1. Simplified schemes of UGT functions in bile acid and eicosanoid catabolism. CDA, chenodeoxycholic acid; HCA, hyocholic acid; HDCA, hyodeoxycholic acid; LCA, lithocholic acid; HETEs, hydroxyeicosatetraenoic acids; 5-HPETE, 5-hydroxyperoxyeicosatetraenoic acid; LTB4, leucotriene B4; PGE2, prostaglandin E2.

Adrenal-generated androgens are present in blood as dehydroepiandrosterone (7 ng/ml) and its sulfate conjugate (311 ng/ml), the latter functioning as androgen storage. Androgens are converted in liver by hydroxysteroid dehydrogenases to both 5α- and 5β-reduced dehydrotestosterone which are mostly conjugated by UGT2B7 at 3-OH to androsterone glucuronide (66 ng/ml) and etiocholanolone glucuronide (36 ng/ml) [29].

2.1.8. UGT2B10

Appears to be highly expressed in human liver [9,11]. It is probably a major UGT conjugating PUFAs and their eicosanoid metabolites (Fig. 1), discussed in Section 4.1. The isoform also conjugates nicotine and other secondary and tertiary amines with higher affinity than UGT1A4 [9,32].

2.1.9. UGT2B15

Is 97% identical with UGT2B17 and important in conjugating androgens and their metabolites such as testosterone and androsterone (together with UGT2B17) [29]. S-Oxazepam has been identified as probe drug for this isoform [13].

2.1.10. UGT2B17

Is conjugating dihydrotestosterone, the active androgen target gene [29]. This highly-regulated gene/protein is involved in conjugating androgens at 17-OH (together with UGT2B15), and may play a critical role in androgen homeostasis in liver but also in target tissue such as testis, skin and prostate [29].

2.2. Role of UGTs in xenobiotic detoxification

The role of glucuronidation in detoxification of xenobiotics has been reviewed [2,6]. In addition to detoxifying roles of UGTs in epithelial barriers and target tissues, hepatic UGTs are mainly involved in systemic clearance of potentially toxic compounds via the biliary tract. For example, tobacco carcinogen detoxification has been studied in detail using tobacco-specific nitrosamines and benzo[a]pyrene (BaP). The major tobacco-specific nitrosamine is metabolized to the UGT substrate NNAL (4-methylnitrosamino)-1-(3-pyridyl)-1-butanol which is N-glucuronidated by UGT1A4 and 2B10 [33] and O-glucuronidated by UGT2B7 and 2B17 [34]. Genetic studies using carriers of the UGT2B17 deletion suggested that this polymorphism is associated with reduced NNAL detoxification and increased individual susceptibility to tobacco-related cancers [34]. BaP is known to be converted to the ultimate carcinogen BaP-7,8-diol-9,10-epoxide. Hepatic UGT1A1 and 1A9 (and extrahepatic UGT1A7 and 1A10) are able to detoxify the intermediate BaP-7,8-diol [35]. It has been demonstrated that a polymorphism of UGT1A7 (UGT1A7*3) reduces UGT1A7 activity and may increase the risk of smoking-related orolaryngeal cancer [36]. Glucuronidation may also reduce tumor promoting oxidative stress mediated by BaP quinone-quinol redox cycles by efficiently conjugating BaP quinols by UGT1A6 and 1A9 [6,37].

3. Overview of factors responsible for interindividual variation of hepatic UGT expression

High interindividual variation of UGT expression was observed in multiple investigations [8,11,38]. Sex differences in UGT activity were found to be relatively small [8]. It is to be expected that the % mean levels of UGT expression listed in Table 1 may change in future studies including larger numbers of individuals. Expression of UGT2B4 was highest in several studies [7,10,11], followed by UGT2B10 and 1A1 in [11], by 2B15 and 2B7 in [10]. Certainly, more comprehensive studies are needed.

Major factors responsible for interindividual variation include (i) UGT genetic diversity including polymorphisms, alternate splicing and epigenetic variation, (ii) liver-enriched transcription factors and (iii) ligand-activated transcription factors, the latter adaptively regulated by exposure to endo- and xenobiotics and discussed in Section 4. Polymorphisms (frequent allelic variants in >1% of the population) are known to contribute to interindividual variation of UGT expression in liver. UGT allelic variants in the coding and regulatory region are updated at the UGT web site at http://www.som.flinders.edu.au/FUSA/ClinPharm/UGT and www.ugtalleles.ulaval.ca. As exemplified by studies of the regulatory region of UGT1A1 implications of polymorphisms are quite complex including distal and proximal motifs; for example, UGT1A1 expression is reduced by the frequent TATA box variant responsible for Gilbert's syndrome and the T3279G mutant in the gtPBREM cluster (discussed in Section 4.2) [39]. Some clinically relevant UGT polymorphisms with implications for cancer risk and cancer therapeutics have been reviewed [8,40]. Knowledge about UGT genetic diversity has recently expanded enormously and its discussion is beyond the scope of the present commentary. An up-to-date comprehensive review on genetic diversity including splice variants has been published [41] but the contribution of genetic diversity to interindividual variation of UGT expression still poses many open questions.

Significant correlation in expression of UGTs to each other has been ascribed to common regulation by liver-enriched transcription factors such as HNF1α (hepatic nuclear factor 1α) and HNF4α [6,11,38,42–44]. The HNF1α represents a homeodomain-containing protein binding to sufficiently similar elements of the palindromic consensus sequence GTTAATNATTAAC in the regulatory region of target genes such as UGT1A9 [43,44]. In contrast, HNF4α is a member of the nuclear receptor family, NR2A1 [45]. Synergistic action of HNF1α and HNF4α on the expression of UGT1A9 has been studied in detail; it was found that the action of HNF4α is dependent upon HNF1α and in crosstalk with a number of nuclear receptors [44]. Certainly, more work is needed to fully understand tissue-specific expression of UGTs.

4. Regulation of UGT expression by ligand-activated transcription factors

Ligand-activated transcription factors mostly belong to the large nuclear receptor superfamily [45]. They bind to cognate response elements of target genes as heterodimers with RXR (retinoid X receptor). Two ligand-activated transcription factors which do not belong to this family (AhR and Nrf2) are discussed first: the AhR (also termed dioxin receptor) belongs to the bHLH/PAS (basic Helix-Loop-Helix/Per-Arnt-Sim) family which binds to XREs (xenobiotic response elements) in target genes as heterodimer with its partner Arnt [46]. The leucine-zipper factor Nrf2 is discussed together with the AhR since these transcription factors share a number of ligands ([47] for references) and exhibit close bidirectional crosstalk [48]. Nrf2 binds to AREs (antioxidant response elements) of target genes as heterodimer with small Maf proteins. Table 2 gives an overview of subsequently discussed ligand-activated transcription factors, their xeno- and endobiotic ligands, and well studied UGTs as target genes.

4.1. Ah receptor/Nrf2: coordinate regulation of respective gene batteries including UGTs

The AhR represents a multifunctional switch which exhibits important roles in metabolism of endo- and xenobiotics, cell proliferation and differentiation, reproduction and development [46]. Genetic studies using mouse strains expressing high- and low-affinity AhR led to the identification of the murine AhR gene battery (Cyp1a1, Cyp1a2, NADPH quinone oxidoreductase-1, aldehyde dehydrogenase 3a1, Gsta1 and Ugt1a6) [49]. AhR-binding XREs appear to be functional in all UGT1 genes [50,51]. In support of this finding, moderately-enhanced glucuronidation of paracetamol (an overlapping substrate of AhR-controlled UGT1A1, 1A6 and 1A9 [21]) was detectable in heavy cigarette smokers (presumably exposed to AhR ligands) [52]. Induction of UGT1A1 by AhR ligands was also observed in human primary hepatocyte cultures [53].

As mentioned before, the Nrf2-mediated antioxidant gene battery exhibits bidirectional crosstalk with the AhR. Detailed studies in mice suggest that expression of most UGT1 and 2 family members depended on both AhR and Nrf2 [48]. In human Caco-2 cells UGT2B7 was induced by the Nrf2 agonist tert-butylhydroquinone but not by the AhR agonist TCDD whereas UGT1A6 and 1A9 were induced by both agonists [54]. Hence, crosstalk between AhR and Nrf2 needs to be clarified in humans. Coordinate induction of these batteries may attenuate oxidative stress generated by AhR activation. Evidence has also been obtained that coinduced Phase I and II enzymes including CYPs and UGTs reduce accumulation of toxic intermediates [55].

Recently, accumulating evidence suggests that AhR is involved in homeostasis of endobiotics such as bilirubin and eicosanoids [56,57]. In concert with CYPs and other enzymes, UGTs may contribute to both local and systemic eicosanoid homeostasis [18,19]. Based on these findings, selected pathways of arachidonic acid (AA) metabolism are discussed (Fig. 1). Multiple CYPs (including AhR-controlled CYP1A1) are involved in omega oxidation of AA to vasoactive 20-HETE (20-hydroxyeicosatetraenoic acid) [58] which is excreted as 20-HETE glucuronide [59], particularly in liver cirrhosis [60]. The relevance of 20-HETE synthesis has been substantiated by epidemiologic studies demonstrating that expression of a 20-HETE-synthesizing CYP4A11 variant is associated with essential hypertension [61]. Both AA and 20-HETE are efficiently conjugated by UGT2B7 [19]. Various lipoxygenases (LOXs) are oxidizing AA to proinflammatory 5-, 12- and 15-HETEs which are inactivated by multiple UGTs including UGT2B4, 2B7 and 2B10 [18]. Moreover, AA is oxidized by 5-LOX via 5-HPETE (5-hydroxyperoxyeicosatetraenoic acid) to proinflammatory LTB4 (leucotriene B4), a good substrate of UGT2B7 [18]. Glucuronidation of LTB4 has been demonstrated in primary cultures of human hepatocytes [62]. Furthermore, COX1/2 are known to generate proinflammatory PGE_2, a substrate of UGT2B7 [19]. Based on lipidomic findings a stepwise increase in LOX metabolites such as 5- and 15-HETE characterizes the progression from normal liver to nonalcoholic fatty liver disease and steatohepatitis [63]. It is tempting to speculate that highly expressed UGT2B4 and 2B10 may have evolved to prevent inflammatory responses of 5- and 15-HETEs under pathophysiological conditions.

4.2. CAR and PXR as transcription factors of UGTs

Induction of bilirubin glucuronidation by phenobarbital is known from early clinical studies. In fact, Crigler–Najjar syndromes I and II have been distinguished on the basis of phenobarbital induction of UGT1A1 [64]. Recently, functional CAR- and PXR-binding response elements have been identified in the gtPBREM cluster of UGT1A1 [65] which also contains response elements for PPARα [66], AhR [67], Nrf2 [68] and the glucocorticoid receptor [65].

CAR (NR1I3) and PXR (NR1I2) are discussed together since they are often activated by overlapping agonists [69], and probably evolved through a common ancestor [70]. However, whereas PXR ligands such as rifampicin directly bind to the transcription factor, activation of CAR by antiepileptic phenobarbital-type inducers (phenobarbital, phenytoin and carbamazepin) occurs by an indirect mechanism. Phenobarbital activates nuclear translocation of CAR by dephosphorylation of its threonine 38 [71]. However, the true 'receptor' of phenobarbital is still unknown.

The role of PXR in detoxification of toxic lithocholic acid has been elegantly demonstrated using PXR-deficient and humanized PXR-transgenic mice [27]. Lithocholic acid activates PXR and induces its target CYP3A4 generating 6-hydroxylated bile acids which are glucuronidated by UGT2B4 (Fig. 1) [72]. Increased excretion of 6-hydroxylated hyodeoxycholic acid glucuronide together with decreased excretion of bile acid sulfates has been demonstrated in rifampicin-treated patients [24] (for discussion see Section 4.4).

Table 2
Selected xeno- and endobiotic activators of transcription factors/xenosensors and UGTs as target genes. *: endobiotic ligand/activator. I (a) and (b), bHLH-PAS and leucine-zipper family members, respectively; II (a)–(d), nuclear receptor superfamily members.

Transcription factor/xenosensor	Xeno- and endobiotic ligands/activators	UGTs as target genes
I (a) AhR	Benzo[a]pyrene TCDD	UGT1 members [48,51,67]
I (b) Nrf2	β-Naphthoflavone Quercetin Eicosanoids* Bilirubin* Sulforaphane β-Naphthoflavone	UGT1 and 2 members [48]
II (a) PXR/CAR	Phenobarbital Phenytoin Carbamazepin Rifampicin Bile acids*	UGT1A1 [65]
II (b) FXR,	Bile acids*	UGT1A3 [89]
II (c) LXR	Bile acids*	UGT1A3 [87]
II (d) PPARα	Fibrates Eicosanoids*	UGT1A1 [66], UGT1A9 [76], UGT2B4 [77]

4.3. PPARα-controlled UGTs in fatty acid, eicosanoid and bile acid metabolism

PPARα (NR1C1) is strongly expressed in liver and activated by a variety of hypolipidemic fibrate drugs (including bezafibrate, ciprofibrate, clofibrate, fenofibrate and gemfibrozil) [73]. Elegant studies demonstrated that PPARα is also activated by polyunsaturated fatty acids and eicosanoids [74,75]. UGT1A1 [66], UGT1A9 [76] and UGT2B4 [77] have been demonstrated to be target genes of PPARα. In transgenic mice UGT1A3 and 1A6 were also identified as controlled by PPARα [66].

4.4. Synergistic regulation of CYPs, SULTs and UGTs in bile acid homeostasis and detoxification by PXR, PPARα, FXR, and LXR

Bile salts are a major pathway for hepatic cholesterol catabolism. They are essential biological detergents that facilitate intestinal absorption of lipids and fat-soluble vitamins. For this purpose human bile acids recirculate 6–10 times per day resulting in a daily bile acid pool of 20–40 g. However, only 0.5 g are lost through fecal excretion [78]. In cholestatic liver disease, bile acids accumulate in hepatocytes leading to liver injury, fibrosis and cirrhosis. Therefore, bile acid homeostasis has to be strictly controlled. Primary bile acids include chenodeoxycholic acid which is converted by intestinal bacteria to toxic lithocholic acid (LCA, Fig. 1). Bile acids are excreted via the bile as sulfate and glucuronide conjugates; in cholestasis these conjugates are also excreted in urine [79]. In cholestatic liver disease these bile acids are either sulfated by CAR-controlled SULT2A1 [80,81] or (after hydroxylation by CYP3A4 to hyocholic and hyodeoxycholic acids) glucuronidated by UGT2B4 and excreted as 6-OH glucuronides (Fig. 1) [24–26]. In addition, bile acids are conjugated at 3-OH by UGT2B7 [82].

Bile acid homeostasis is achieved by a network of lipid-sensing nuclear receptors (CAR, PXR, PPARα), cholesterol-sensing LXR (liver X receptor; NR1H3) and bile acid-sensing FXR (farsenoid X receptor; NR1H4) and a number of lipid-metabolizing enzymes (CYP3A4, CYP7A1, SULT2A1 and UGTs) [84,85]. These lipid-sensing nuclear receptors are activated by bile acids and by drugs such as rifampicin, activating PXR [24–26] and by fibrates, activating PPARα [74]. FXR and PXR strongly downregulate CYP7A1, the rate limiting enzyme in bile acid synthesis [83,84] and upregulate CYP3A4-mediated 6-hydroxylation of bile acids which are subsequently glucuronidated by PPARα-inducible UGT2B4 (Fig. 1) [24–26]. These reactions may in part be responsible for attenuating pruritus in rifampicin-treated cholestatic patients [85].

Intriguingly, chenodeoxycholic and lithocholic acid can also be detoxified in vitro by LXR- and FXR-induced UGT1A3 which forms C24-ester glucuronides (Fig. 1) [86–89]. However, under physiologic conditions bile acids are mostly conjugated at C24 with glycine or taurine, and the resulting conjugates recirculate as bile acid pool of 40–80 g/day. UGT1A3-mediated C24-ester glucuronide formation is enhanced under cholestatic conditions. Interestingly, bile acids with shorter side chain such as norursodeoxycholic acid are efficiently conjugated by UGT1A3 to C23-ester glucuronides [90]. Certainly, more work is needed to elucidate the complex network responsible for bile acid homeostasis and detoxification.

5. General and evolutionary aspects on UGTs and their transcription factors

UGTs are part of a lipid-metabolizing defense system including CYPs, conjugation enzymes, conjugate transporters and lipid-sensing transcription factors. This defense system was already present in simple multicellular organisms such as the sea urchin [3]. Drugs are part of the handled lipids by this system although for humans arguably the most important part. With regard to conjugation of alcoholic and phenolic OH groups sulfation often competes with glucuronidation, whereby SULTs often exhibit higher affinity but lower capacity than UGTs. The complexity of differential regulation of SULTs and UGTs is suggested by their CAR and PXR control, respectively, discussed in Section 4.4. In addition, sulfate conjugates often represent storage forms as in the case of dehydroepiandrosterone sulfate [29]. Studies of tissue-specific expression profiles of nuclear receptor superfamily members revealed a hierarchical network affecting distinct physiological pathways including lipid metabolism [91]. Light/dark cycling of nuclear receptors suggests that fundamental concepts such as constitutive and adaptive gene expression may require reexamination [92]. This notion is supported by many examples showing that often constitutive expression is lost in ligand-activated transcription factor knockout mice [93]. When reflecting about factors responsible for interindividual variation of hepatic UGTs one should bear in mind that the discussed transcription factors are again under control of higher order transcription factors. For example, both the AhR and the CAR are controlled by the β-catenin pathway [94].

A number of pro- and antiinflammatory signals are substrates of UGT2B4, 2B7 and 2B10, for example, 5-, 12-, 15-, 20-HETE and LTB4 [18,19]. In addition, accumulating evidence suggests autoregulatory feedback loops between ligands of transcription factors and metabolism of these ligands by CYPs. Similarly, UGT1A1 detoxifies the AhR activator bilirubin [57,58], and UGT2B7 detoxifies AhR activators such as metabolites of proinflammatory 12-HETE and LTA4 [95,96]. In addition, UGT2B4 is involved in conjugation of bile acids which are activators of PXR [24–26] and PPARα [73]. Based on these observations it is tempting to speculate that high hepatic levels of hepatic UGT2B4 and 2B10 may have been necessary to protect the liver and the whole organism against cholestasis and inflammatory diseases [63].

6. Conclusions

The commentary was stimulated by the first study examining expression of all human adult hepatic UGTs [11]. This study identified five substantially expressed UGT1 family members (UGT1A1, 1A3, 1A4, 1A6 and 1A9) and five UGT2 family members (UGT2B4, 2B7, 2B10, 2B15 and 2B17). Large interindividual variability of UGT expression was observed in several investigations [7–11]. The results need to be confirmed through studies of larger numbers of individual livers. Advantages and limitations of liver bank studies have been discussed, including quality of liver specimen and insufficient history of recent prescription drugs, alcohol and tobacco use and characterization of UGT polymorphisms [8]. Notably, contribution of genetic diversity including functional polymorphisms to interindividual variation of UGT expression is not in the scope of the present commentary. A significant correlation between expression of different UGTs to each other was attributed to common control by liver-enriched factors such as HNF1α and HNF4α [11,43]. Surprisingly, UGT2B4 and 2B10 were found to be abundant UGT isoforms [7,10,11].

As a first step to better understand the large interindividual variability and rank order of hepatic UGT expression, ligand-activated transcription factors were discussed, including AhR and members of the nuclear receptor superfamily (CAR, PXR, PPARα, FXR and LXR). UGTs of family 2, in particular UGT2B4, 2B7 and 2B10 are involved in the inactivation of a number of pro- and antiinflammatory signals such 5-, 12-, 15-, 20-HETE and LTB4 [18,19]. Similar to CYPs, UGTs appear to be involved in negative autoregulatory feedback loops, for example UGT1A1 controlling

AhR-activating bilirubin [57,58], and UGT2B4 controlling PPARα-activating HETEs [74]. However, more work is needed on factors regulating UGT2B10. Multiple CYPs, SULT2A1 and UGTs are involved in bile acid homeostasis and detoxification. Hence, it is tempting to speculate that in particular the highly expressed UGT2B4 and 2B10 are involved in homeostasis of eicosanoids and bile acids to prevent liver injury in cholestasis, inflammatory diseases and stressful conditions such as starvation or overfeeding, the latter leading to steatohepatitis [63].

Certainly, studies of a larger number of well characterized individual livers are needed to substantiate the discussed % means of hepatic UGT expression levels. Better understanding of the factors responsible for UGT expression and their crosstalk may help to understand inflammatory liver diseases and to improve drug therapy.

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