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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.