UDP-Glucuronosyltransferase Genetic and Drug Responses

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UDP-glucuronosyltransferases (UGTs) are phase II drug-metabolizing enzymes that metabolize endogenous fatty acids such as arachidonic acid metabolites, as well as many prescription drugs, such as opioids, antiepileptics, and antiviral drugs. The UGT1A and 2B genes are highly polymorphic, and their genetic variants may affect the pharmacokinetics and hence the responses of many drugs and fatty acids.

Keywords: metabolism ; drug toxicity ; genetic variants ; UGTs

1. Overview

UDP-glucuronosyltransferases (UGTs) are phase II drug-metabolizing enzymes that metabolize endogenous fatty acids such as arachidonic acid metabolites, as well as many prescription drugs, such as opioids, antiepileptics, and antiviral drugs. The *UGT1A* and *2B* genes are highly polymorphic, and their genetic variants may affect the pharmacokinetics and hence the responses of many drugs and fatty acids. This study collected data and updated the current view of the molecular functionality of genetic variants on *UGT* genes that impact drug responses and the susceptibility to human diseases. The functional information of *UGT* genetic variants with clinical associations are essential to understand the inter-individual variation in drug responses and susceptibility to toxicity.

2. UDP-Glucuronosyltransferase

The UDP-glucuronosyltransferase (UGT) enzymes are phase II drug-metabolizing enzymes that catalyze the glucuronidation reaction. This chemical reaction involves the formation of a covalent bond between the endogenous polar glucuronic acid with drugs and endogenous lipophilic compounds [1]. The glucuronidated compounds have chemical functional groups that accept glucuronic acid. These functional groups include hydroxyl, carboxylic acid, amine, and thiol [2]. The UGTs glucuronidate endogenous compounds, such as bilirubin, bile acids, and steroid hormones. Additionally, the UGTs glucuronidate exogenous compounds such as opioid analgesics, non-steroidal anti-inflammatory agents (NSAIDs), anticonvulsants, and antiviral drugs [3].

Glucuronidation mainly terminates and enhances the elimination of chemical compounds by enhancing their solubility in urine. Additionally, glucuronidated compounds are large, which favors their elimination through biliary excretion [4]. Therefore, the glucuronidation reaction can increase the efficacy and toxicity of some drugs, and glucuronide morphine is reportedly 100 times more potent than the morphine substrate itself [5].

Glucuronidation occurs in mammalian species, although significant inter-species differences exist in the rate of glucuronidation, expression, and selectivity [6]. For example, codeine is glucuronidated at higher rates among humans than rats [7][8]. Additionally, cat livers cannot glucuronidate the analgesic paracetamol drug [9]. Therefore, any information obtained about glucuronidation in animals is not directly applicable to humans.

3. Expression of UGT Isoforms

The liver has the greatest abundance of UGT expression [10][11]. UGTs 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 play major roles in the glucuronidation of drugs in the liver. Additionally, the UGT1A and 2B subfamilies are also expressed in the kidneys, small intestine, colon, stomach, lungs, epithelium, ovaries, testes, mammary glands, prostate, and heart [12][13]. The UGT3 family is not expressed in the liver; it is mainly expressed in the thymus, testes, and kidneys [14]. Therefore, the UGT3 family members are considered extrahepatic UGT enzymes. The UGT2B subfamily isoforms are expressed at higher rates than the UGT1A subfamily isoforms [10][11][13]. UGTs are transmembrane proteins located in the smooth endoplasmic reticulum of cells [15].

Many transcriptional factors can regulate the expression of UGT genes. Hepatocyte nuclear factors (HNFs) 1 and 4, the aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), pregnane X receptor (PXR), farnesoid X receptor (FXR), liver X receptor (LXR), and peroxisome proliferator-activated receptors (PPARs) regulate the expression of UGTs in the liver and other tissues [3][16][17]. CAR induces *UGT1A1* and PXR regulates the expression of the *UGT1A1*, *1A3*, *1A4*, and *1A6* genes [18][19]. Activation of FXR upregulates *UGT2B4* and downregulates *UGT2B7* [20][21] and LXR induces the expression of the *UGT1A3* gene [22]. PPARα regulates the expression of the *UGT1A1*, *1A3*, *1A4*, *1A6*, *1A9*, and *2B4* genes in a tissue-specific manner [23]. Furthermore, the *UGT1A1*, *1A3*, *1A4*, *1A6*, and *1A9* genes are upregulated after the activation of AhR nuclear receptor ligands, such as polycyclic aromatic hydrocarbons [24]. Steroid hormones are regulators of UGT expression in the breast and prostate, and 19β-estradiol and dihydrotestosterone increase the expression of UGT genes responsible for glucuronidation of androgens [25]. Furthermore, Jarrar et al. (2019) showed that NSAIDs downregulated the mRNA expression of the mouse *ugt2b1* gene in the liver and kidneys and upregulated the expression of *ugt2b1* in the heart. However, the underlying mechanisms of how NSAIDs regulate the expression of *ugt2b1* in an organ-specific manner remain to be investigated [6].

4. The Role of UGTs in Xenobiotic Metabolism

UGT1A1, 1A3, 1A4, 1A6, 1A9, and 2B7 play major roles in drug metabolism in humans [3]. UGT1A1 glucuronidates R-carvedilol [26], etoposide [27], B-estradiol [28], ezetimibe [29], and the active metabolite of irinotecan, SN-38 [30]. UGT1A3 glucuronidates ezetimibe [31] and telmisartan [32]. UGT1A4 glucuronidates amitriptyline [33], lamotrigine [34], midazolam [35], olanzapine [36], and trifluoperazine [37]. UGT1A6 metabolizes deferiprone [38] and paracetamol [39] and UGT1A9 glucuronidates propofol [40], entacapone [41], indomethacin [42], mycophenolic acid [43], and oxazepam [44]. UGT2B7 metabolizes carvedilol [26], codeine [45], diclofenac [42], epirubicin [46], flurbiprofen [42], morphine [47], naloxone [48], and zidovudine [49], while UGT2B15 glucuronidates lorazepam [50] and oxazepam [44].

Glucuronidation of certain drugs, such as cyclooxygenase (COX)-2 selective NSAIDs rofecoxib and celecoxib, requires a hydroxyl group on the drug, which is obtained through a cytochrome P450 (CYP450) oxidative reaction [51][52]. However, glucuronidation of many drugs, such as morphine, can be done without the need for the CYP450 oxidation reaction [47].

UGTs also play a role in the metabolism of phytochemical compounds. For example, glycyrrhetinic acid, which is found in licorice, is glucuronidated through UGT1A1, 1A3, 2B4, and 2B7 [53]. The hepatotoxic alkaloid senecionine is glucuronidated by UGT1A4 [54]. This herbal metabolism by UGTs forms part of the drug–herb interaction and influences the metabolism and hence the efficacy of the drugs.

5. Conclusions

Chemical inhibition and genetic variants of the UGT genes play important roles in the drug response, toxicity, and susceptibility to human diseases. However, clinical evidence has shown that the UGT1A1 isoform genetic variants can be considered biomarkers for drug responses and susceptibility to diseases. Additionally, inhibition of endogenous glucuronidation can lead to an imbalance in the levels of endogenous fatty acids and steroidal hormones and cause human diseases. Further clinical studies are needed to validate the clinical impacts of the UGT1A and UGT2B genes for personalized medicine and human diseases.

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