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The role of glucuronidation in drug resistance

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ABSTRACT

The final therapeutic effect of a drug candidate, which is directed to a specific molecular target strongly depends on its absorption, distribution, metabolism and excretion (ADME). The disruption of at least one element of ADME may result in serious drug resistance. In this work we described the role of one element of this resistance: phase II metabolism with UDP-glucuronosyltransferases (UGTs). UGT function is the transformation of their substrates into more polar metabolites, which are better substrates for the ABC transporters, MDR1, MRP and BCRP, than the native drug. UGT-mediated drug resistance can be associated with (i) inherent overexpression of the enzyme, named intrinsic drug resistance or (ii) induced expression of the enzyme, named acquired drug resistance observed when enzyme expression is induced by the drug or other factors, as food-derived compounds. Very often this induction occurs via ligand binding receptors including AhR (aryl hydrocarbon receptor) PXR (pregnane X receptor), or other transcription factors. The effect of UGT dependent resistance is strengthened by coordinate action and also a coordinate regulation of the expression of UGTs and ABC transporters. This coupling of UGT and multidrug resistance proteins has been intensively studied, particularly in the case of antitumor treatment, when this resistance is "improved" by differences in UGT expression between tumor and healthy tissue. Multidrug resistance coordinated with glucuronidation has also been described here for drugs used in the management of epilepsy, psychiatric diseases, HIV infections, hypertension and hypercholesterolemia. Proposals to reverse UGT-mediated drug resistance should consider the endogenous functions of UGT.

Contents

Abbreviations: ABC, ATP-binding cassette; ADME, absorption, distribution, metabolism, excretion; AED, antiepileptic drug; AhR, aryl hydrocarbon receptor; ARNT, AhR nuclear translocator; ARV, antiretroviral drug; BBB, blood–brain barrier; BCRP, breast cancer resistance protein; CAR, constitutive adrostane receptor; CNS, central nervous system; CPT-11, irinotecan; CYP, cytochrome P450; DME, drug-metabolizing enzymes; GLI1, glioma-associated protein, sonic hedgehog transcription factor; GSH, gluthatione; HIV, human immunodeficiency virus; IMS, immunosuppressive drug; MDR, multidrug resistance; MPA, mycophenolic acid; MRP, multidrug resistance-associated protein; NBD, nucleotide (ATP)-binding domains; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PXR, pregnane X receptor; RXR, retinoid X receptor; SN-38, irinotecan active metabolite; SNP, single nucleotide polymorphism; TMD, transmembrane domain; UDP, uridine diphosphate; UDPGA/UDPGlcUA, UDP-glucuronic acid; UGT, UDP-glucuronosyltransferase.

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1. Introduction

1.1. UGT function in phase II metabolism

Enzymatic systems are necessary to transform nonpolar endogenous and exogenous compounds into their hydrophilic derivatives. This metabolism aims to impair the undesired accumulation of lipophilic agents, facilitating their excretion outside the organism or out of cells. The majority of exogenous compounds (xenobiotics) undergo phase I metabolism, which leads to more polar and more reactive compounds. They are prepared to be better substrates for phase II metabolic enzymes. However, the substrates for phase II metabolic enzymes are not only xenobiotics, but also many endogenous compounds that play crucial functions in the organism. Phase II enzymes catalyze substrate metabolism to more polar products by the conjugation with glucuronic acid, sulfate, glutathione or amino acids, which influences pharmacokinetics and the final biological effects of the metabolized agents (Nagar & Blanchartd, 2006).

Conjugation of uridine-5′-diphospho-α-D-glucuronic acid (UDPGA) with the functional group of aglycone (hydroxyl, amine, carboxyl, sulfhydryl), seems to be crucial among phase II metabolic pathways (Fig. 1). Uridine 5′-diphospho-glucuronosyltransferase isoenzymes (UGTs, originally called UDPGTs) catalyze this type of conjugation, which occurs according to type 2 nucleophilic substitution, S_N2, and leads to the formation of β-D-glucuronides. Glucuronides are hydrophilic compounds due to the presence of hydroxyl groups and a dissociated carboxyl group at physiological pH. Thus, they are able to be excreted by active transport systems and eliminated. As a consequence, the first biological function discovered for UGTs was deactivation and detoxification of their substrates. Endogenous UGT substrates are bilirubin, bile acids, lipid acids, steroid and thyroid hormones and lipid soluble vitamins. In this case glucuronidation acts as a control to maintain their appropriate level in the organism in order to avoid physiological disturbances (Bock, 2012, 2014). The main exogenous UGT substrates are environmental pollutants, carcinogenic compounds and numerous groups of therapeutic agents. Thus, UGT enzymes belong to the family of drug metabolizing enzymes, DME (Rowland et al., 2013).

The superfamily of human UGT proteins is composed of 22 functional isoenzymes, which are classified into four gene families (UGT1, UGT2, UGT3 and UGT8) (Fig. 2) according to sequence similarity (Mackenzie et al., 2005). The enzymes that are most efficient at using UDPGA/UDPGlcUA as the glucosyl donor are the members of UGT1 and UGT2 families. These families are strongly engaged in drug metabolism. Members of the UGT3 family are found primarily in the thymus, testis and kidney, but are undetectable in the liver and gastrointestinal tract. Moreover, the sugar substrates for UGT3 are demonstrated to be UDPGlcNAc (N-acetylated UDPGlcUA) and UDPGal (in which the glucuronic acid of UDPGlcUA is substituted with galactose) instead of UDPGA. Available evidence suggests that this UGT family does not play a significant role in detoxification of xenobiotics (Mackenzie et al., 2011). In turn, the only known member of the UGT8A family, UGT8A1 is an UDP galactose ceramide galactosyltransferase, which uses UDPGal as a cofactor, and similarly has not been observed to participate in drug metabolism (Rowland et al., 2013).

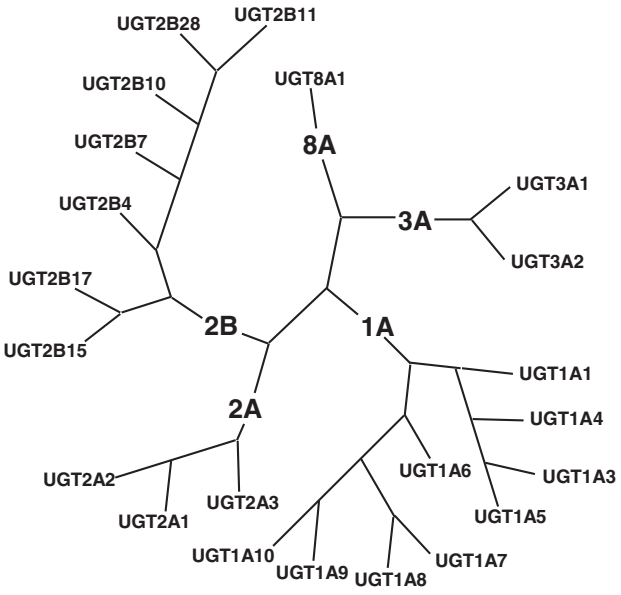

Fig. 2. Phylogenetic tree of the 22 human UGT isoenzymes. The UGT superfamily is categorized into 4 families and 5 subfamilies: UGT1A, UGT2A, UGT2B, UGT3A and UGT8A on the basis of sequence identity. Members of the UGT1 and UGT2 families are the most effective in using UDPGA as a substrate and play a key role in glucuronidation of drugs. Members of the UGT3 and UGT8 families prefer to use other UDP-sugars and their contribution to drug metabolism is insignificant (based on Rowland et al. (2013)).

It is well known that the liver has the greatest abundance and array of UGT enzymes (Court et al., 2012). Besides hepatic expression, UGT1A and UGT2B enzymes are present in the kidneys, small intestine, colon, stomach, lungs, epithelium, ovaries, testis, mammary glands and prostate (Court et al., 2012; Ohno & Nakajin, 2009). The most important sites of extrahepatic metabolism are the kidneys and gastrointestinal tract (Knights & Miners, 2010). The majority of members of the UGT1 and UGT2 families are expressed in the human liver, except for UGT1A5, 1A7, 1A8, 1A10 and 2A1. Members of the UGT2B family are more abundant than members of the UGT1A family and UGT2B4 levels in the human liver are the highest of all UGT isoenzymes. Total UGT mRNA expression in the small intestine is estimated as one-seventh of that of adult liver and UGT2B7, 2B17, 1A10 and 1A1 expression is 20%, 19%, 17% and 13%, respectively, of total UGT mRNA in the small intestine. Among different UGT isoforms, UGT1A10 and UGT1A8 are specifically expressed in the intestines, although the expression of UGT1A8 is 22-fold lower than of UGT1A10. Apart from the liver and intestines, high levels of UGT, especially UGT2B15, 2B17 and 1A6 are present in the stomach, whereas UGT2B7, 1A9 and 1A6 are present in the kidney (Court et al., 2012; Oda et al., 2015; Rowland et al., 2013). Little is known of the spatial structure of UGTs. UGT2B7 was the first isoenzyme,

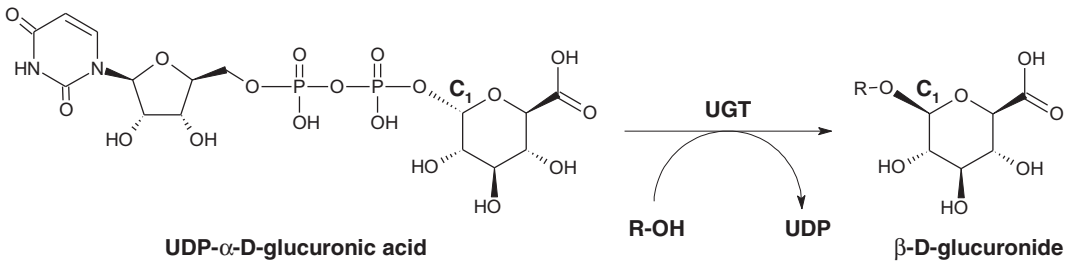

Fig. 1. Glucuronidation reaction. Nucleophile R-OH attacks anomeric carbon atom C1 of glucuronic acid by nucleophilic substitution mechanism S_N2 leading to the inversion of C1 configuration from α in UDP-glucuronic acid to α in the glucuronide.