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Biochemical Pharmacology 66 (2003) 691–696
Commentary
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Vertebrate UDP-glucuronosyltransferases: functional and evolutionary aspects

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Abstract

UDP-glucuronosyltransferases (UGTs) represent major phase II drug metabolizing enzymes. They are part of a rapidly growing, sequence similarly based superfamily of UDP-glycosyltransferases, including a number of enzymes, which presumably are functionally unrelated to UGTs. The present commentary discusses evolutionary aspects of the large glycosyltransferase superfamily emphasizing functionally related members which share roles in detoxication and elimination of endo- and xenobiotics. The discussion starts with the two human UGT families and polymorphism frequencies in different populations. These families probably evolved in vertebrates as a result of the struggle against toxic phytoalexins at the hepatogastrointestinal barrier. Co-regulation of some UGTs with other drug metabolizing enzymes may also have evolved in the course of 'animal–plant warfare'. Related UDP-glucosyltransferases evolved in insects. Even in plants and bacteria UDP-glucosyltransferases have been characterized which may be functionally related.

Keywords: Vertebrate UDP-glucuronosyltransferases; Drug metabolizing enzymes; Gastrointestinal barrier; Co-regulation of CYPs and UGTs; UDP-glycosyltransferase superfamily

1. Introduction

UGTs represent major phase II drug metabolizing enzymes (DMEs), conjugating a wide variety of drugs, dietary phytoalexins, and endobiotics, such as bilirubin and steroid hormones. They often work in concert with other DMEs to convert lipid-soluble compounds into water-soluble and excretable forms (Fig. 1). Lipophilic endo- and xenobiotics (X) enter cells by passive diffusion or uptake transporters (often termed phase 0). Phase I enzymes, mainly cytochromes P-450 (CYPs), convert them into nucleophilic phenols and polyphenols or electrophiles, such as quinones and epoxides, which are then conjugated by phase II enzymes, such as UGTs and SULTs or GSTs, respectively. The resulting organic anions are removed from the cell by export transporters (phase III) [1]. A number of DMEs rapidly interconvert nucleophiles and electrophiles, for example, NQO1 and peroxidases. The balance between phase I and II enzymes often determines the accumulation of reactive intermediates which may cause oxidative/electrophile stress and toxicity, the latter often initiated by covalent binding of metabolites to DNA and protein. Hence, when dealing with UGT functions, glucuronide transporters and compensatory enzymes, such as SULTs and other DMEs, have to be taken into account.

In humans more than 16 UGTs have been characterized and subdivided into two families [2,3]. All family 1 members are encoded by a unique UGT1 locus present on chromosome 2q37. In this gene locus 13 first exons, each preceded by its own promoter and enhancer regions, are spliced to identical exons 2–5 which encode the C-terminal part of the protein responsible for binding UDP-glucuronic acid. The UGT1 locus may have evolved by a unique set of exon 1 duplications. In contrast, genes of family 2 members are clustered on human chromosome 4q13 and probably evolved by gene duplication. Currently, a growing number of polymorphisms of these two UGT families are being characterized [2,3] which are invaluable to elucidate the function of UGT isoforms in predisposing individuals to abnormal drug reactions [4] and to toxin-mediated disease [5].

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Abbreviations: UGT, UDP-glucuronosyltransferase; DME, drug metabolizing enzyme; CYP, cytochrome P-450; NQO, NADPH quinone oxidoreductase; SULT, sulfotransferase; GST, glutathione *S*-transferase; MRP, multidrug resistance protein; GI, gastrointestinal; AhR, arylhydrocarbon receptor; PAH, polycyclic aromatic hydrocarbon.

0006-2952/$ – see front matter
doi:10.1016/S0006-2952(03)00296-X

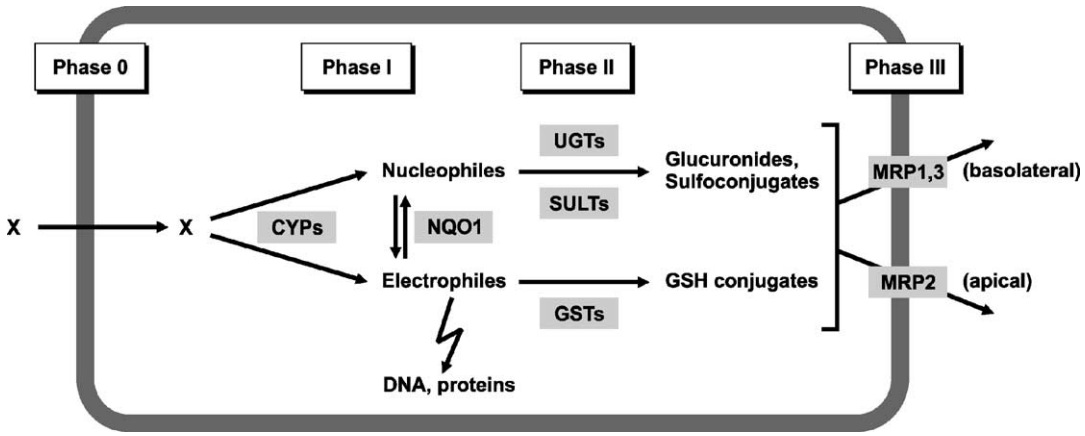

Fig. 1. Schematic illustration of cellular endo- and xenobiotic biotransformations. CYPs, cytochromes P-450; NQO1, NADPH quinone oxidoreductase-1; UGTs, UDP-glucuronosyltransferases; SULTs, sulfotransferases; GSTs, glutathione *S*-transferases; GSH, glutathione; MRPs, multidrug resistance proteins.

The evolutionary role of UGTs is evident at the hepato-gastrointestinal barrier, where vertebrates have to detoxify numerous dietary plant phytoalexins (Fig. 2). Phytoalexins are antimicrobial compounds generated in plant cells exposed to microorganisms. They are also important in protecting plants against insects and other animal predators. Many of them act as polyphenolic pro/antioxidants, such as quercetin, present, for example, in onions and chrysin in honey [6], anthocyanidine, the red color of roses [7], the phytoestrogen resveratrol in grapes and wine [8], and zeaxanthin in bacteria [9]. They are stored in plant cells and bacteria as glucosides which are readily hydrolyzed in the gastrointestinal (GI) tract. The protective role of UGTs is underscored by their large numbers and high expression levels in liver and GI tract mucosa, including selective expression of some UGTs, such as UGT1A7 in the upper GI tract (orolaryngeal mucosa, esophagus, and stomach) and of UGT1A8 and 1A10 in the small intestinal and the colon mucosa [10]. This protective function may have been most relevant at earlier stages of evolution when fish and terrestrial animals tried to live on a plant diet, and plants developed phytoalexins for survival, a process termed 'animal–plant warfare' [11]. The commentary mainly focuses on the conserved vertebrate UGT1 gene locus and on functionally related UDP-glucosyltransferases in insects, plants, and bacteria.

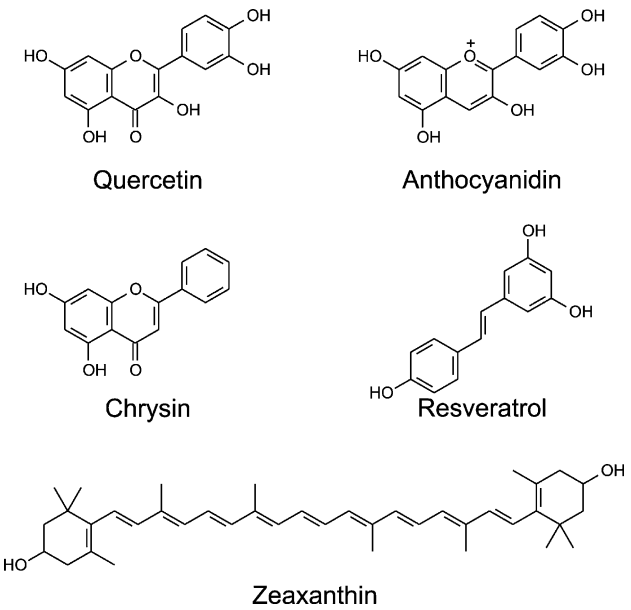

Fig. 2. Chemical structures of discussed phytoalexins and antioxidants.

2. Functions of human UGT isoforms: roles of UGT polymorphisms

Some general aspects of UGT activity are discussed first. UGTs function at several levels in the organism: in pre-systemic or systemic drug metabolism and locally within cells. It is known that a number of factors control glucuronide formation and disposition in cells and in the whole organism. Nevertheless, when using isoform-specific probe substrates, *in vitro* microsomal UGT activity correlates well with *in vivo* glucuronide formation. For example, the interindividual hepatic bilirubin UGT activity correlated with the blood level of bilirubin in Gilbert individuals [12] and the morphine UGT activity with presystemic glucuronidation of oral morphine [13]. Locally, UGT activity has been shown to be important, for example, in controlling steroid hormone levels [14]. Hence, *in vitro* analysis of UGT activity is relevant for prediction of *in vivo* metabolic clearance [15,16].

Several polymorphisms have been discovered in UGT families 1 and 2 [2,3]. In the UGT1 locus a TATA box mutation of bilirubin-conjugating UGT1A1 (UGT1A1*28), leading to decreased enzyme activity, has received a lot of interest since it is frequently associated with Gilbert's syndrome in Caucasians [17,18]. In addition to be exposed to mild hyperbilirubinemia, Gilbert individuals have been shown to be predisposed to the unwanted side effects of the chemotherapeutic agent irinotecan since its effective major

metabolite SN38 is mostly inactivated by UGT1A1 [4,19]. Repeated sequences, such as $A(TA)_nTAA$, in the promoter of UGT1A1 are intrinsically unstable and tend to lengthen or shorten as a result of unequal crossing over in meiosis. It has been shown that increasing TA repeats of the UGT1A1 TATA box lead to reduced transcription, enzyme level, and activity [20]. The allelic variants $A(TA)_6TAA$ (UGT1A1*1) and $A(TA)_7TAA$ (UGT1A1*28) are frequent in different populations. A 'balanced polymorphism' has been proposed as a possible explanation for the persistence of the UGT1A1*28 variant [20,21]. Bilirubin may be both deleterious or beneficial; severe hyperbilirubinemia in neonates is known to cause kernicterus and brain damage. On the other hand, low bilirubin together with high biliverdin reductase activity appears to be a powerful antioxidant [22]. In fact, Gilbert individuals seem to be protected from coronary heart disease [23]. There are still major differences in allele frequencies among ethnic groups. For example, the frequency of UGT1A1*28 was found to be ca. 0.29 in Caucasians and 0.26 in Egyptians [24] and only ca. 0.09 in Japanese [21]. Hence, these allelic variants may have been generated relatively recently.

Other polymorphisms have been identified in the UGT1 gene locus, such as allelic variants of the phenol UGT1A6 and 1A7. In particular, an allelic variant of UGT1A7 (UGT1A7*3), expressed in oral mucosa, has been shown to be associated with a marked reduction of benzo(*a*)pyrene phenol UGT activity [25]. Interestingly, this variant was found to be frequent in smokers who develop orolaryngeal cancer [5], underlining the protective role of UGTs. Allelic variants of the three UGT1 isoforms with reduced function can be present at the same chromosome, and in fact frequent co-occurrence of UGT1A1*28, UGT1A6*2, and UGT1A7*7 (haplotype II) has been identified in Caucasians and Egyptians [24]. This linkage disequilibrium has to be taken into account in studies on the association of abnormal drug reactions and toxin-mediated diseases with UGT allelic variants.

3. Evolution of the UGT1 gene locus in vertebrates

The unique UGT1 gene locus reveals a very similar organization in human and rat (Fig. 3). Therefore, it must have been present before the radiation of rodents and man, before the beginning of the Paleocene, i.e. 65 million years ago [26]. Evidence for this gene locus was also obtained in other mammalian species, for example, mouse, rabbit, monkey, dog, and sheep [3]. Herbivorous lagomorphs even evolved duplicated UGT1A6 genes in their UGT1 locus [27]. A major evolutionary driving force for the generation of the UGT1 locus may have been the struggle to detoxify dietary plant polyphenolic phytoalexins [11] or phytoestrogens, such as resveratrol (resembling β-estradiol in structure) [8]. Obviously, sex hormone-like phytoestrogens critically determine reproduction of organisms. Prey–predator adaptations represent a major scenario in evolution. For example, herbivorous predators had to evolve phytoalexin detoxifying enzymes. However, these adaptively generated phenol UGTs were no longer necessary in carnivorous Feliform species because their prey (cattle, sheep, etc.) had already done the job of detoxifying phytoalexins. In fact, in carnivorous cats and leopards UGT1A6 was found to be present as a pseudogene [28].

It is conceivable that the evolution of the two UGT families took place during the evolution of fish species in the Devonian period, about 400 million years ago [26]. One PAH-inducible phenol UGT has been characterized in the teleost plaice (*Pleuronectes platessa*) which was distinct from other UGT activities [3,29,30]. Evidence for multiple UGT gene families, including dioxin-inducible UGTs [31], was also obtained in the zebrafish (*Brachydanio rerio*) [32]: six of these genes were related to mammalian UGT families 1 and 2. However, family 1-related UGTs did not share a common 3′ sequence. Hence, the unique UGT1 locus was not yet evolved in fish. It is conceivable that it was generated in species trying to live mainly on a plant diet when living on land. Glucuronidation has been

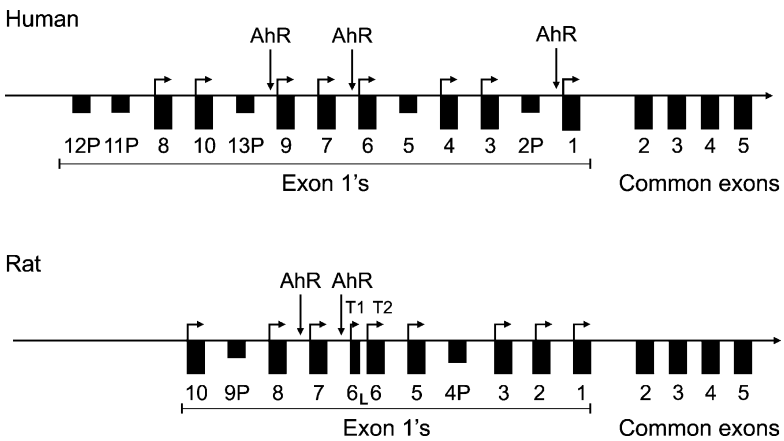

Fig. 3. Organization of the human and rat UDP-glucuronosyltransferase-1 gene locus ([40,42,56–60] and [39,61], respectively). P, pseudogenes; T1, transcription unit 1; T2, transcription unit 2; 6_L, untranslated leader sequence of UGT1A6.

detected in amphibians, reptiles, and birds [33], but UGT sequences from these species are still lacking.

4. Co-regulation of some UGTs with CYPs

Early observations suggested co-regulation of UGTs and CYPs by prototypical phenobarbital- and 3-methylcholanthrene-type inducers [34–37]. Recently, these observations were established in the case of CYP2B/3A and UGT1A genes controlled by the nuclear pregnane X receptor and the constitutive androstane receptor [38]. In addition, co-regulation of both rat and human CYP1A1 and UGT1A6 (and other UGT1 genes, Fig. 3) by the AhR was demonstrated [39,40]. Co-regulation facilitates detoxication of plant phytoalexins and dietary PAH contaminants, such as benzo(*a*)pyrene. For example, phenols generated by induced CYP1A1 can be more efficiently detoxified by co-induced phenol UGTs. In fact, utilizing the Ames test it was shown that co-regulation of CYPs and UGTs attenuates the mutagenicity of benzo(*a*)pyrene [41]. Species differences in transcriptional regulation of UGTs are well known. Nevertheless, in the case of the UGT1 locus even the promoter sequences of some genes may be partly conserved. For example, part of the UGT1A6 promoter region appears to be conserved between rats and humans. Organization of one of the two transcription units of rat UGT1A6 containing a consensus HNF1-binding site (T2, indicated in Fig. 3) appears to be similar to the human transcription unit [42].

In addition to co-regulation of phase I and II DMEs (termed bifunctional induction), another induction mechanism evolved in the course of 'animal–plant warfare' which preferentially induces phase II enzymes, such as GSTs and UGTs (monofunctional induction) [43]. The responsible signaling pathway does not use a receptor but oxidative/electrophile stress [44]. Interestingly, 'monofunctional induction' is triggered by the same polyphenolic phytoalexins, such as the flavonoid quercetin, which are stored in plants as glucosides. There is currently a lot of interest in selective phase II induction by these dietary phytoalexins in the efforts for chemoprotection against diseases [44]. Even organic anion export transporters appear to be co-regulated with phase II enzymes [45,46]. Co-regulation of DMEs by common transcription factors is an important phenomenon. It emphasizes that these enzymes operate in a concerted manner, i.e. as an adaptive biotransformation system, including phase I–III DMEs (Fig. 1).

5. The UDP-glycosyltransferase supergene family: UDP-glucosyltransferases functionally related to UGTs in insects, plants, and bacteria

Using a signature sequence (probably encoding the UDP-binding site) a large and growing UDP-glycosyltransferase supergene family was defined solely on sequence similarity, including enzymes found in insects, worms, yeasts, plants, and bacteria [2]. However, many of these enzymes may be functionally unrelated to UGTs; for example, the interesting ceramide glycosyltransferase 8, found in human, rat, and mouse which is certainly not a DME [3]. Vertebrate UGTs preferentially use UDP-glucuronic acid, although the preference is not absolute. For example, human UGT1A1 accepts UDP-xylose and to a minor extent UDP-glucose [47], UDP1A6 accepts UDP-galacturonic acid and to a minor extent UDP-glucose [48], and UGT2B7 clearly accepts UDP-glucose [49,50].

Slugs [33] and insects [51] are known to form phenobarbital-inducible phenolic glucosides. Recently, an insect phenol UDP-glucosyltransferase has been characterized in the silkworm (*Bombyx mori*) which is probably involved in detoxication of plant phytoalexins [52]. The enzyme was present in the fat body, midgut, and integument and is probably bound to endoplasmic reticulum membranes similar to vertebrate UGTs. It was found to conjugate a number of phytoalexins and simple phenols as well as a number of odorants, such as vanillin, eugenol, β-citronellol, and isomenthol. The latter findings suggest a role of this enzyme in olfaction, similar to vertebrate olfactory UGT2A1 [2]. Interestingly, UDP-glycosyltransferases were detected in insect antenna, although their function has not yet been characterized [53]. In addition, a secretable baculovirus ecdysteroid UDP-glucosyltransferase was identified and characterized [54,55] which was presumably acquired from an insect host. Ecdysteroids are involved in the regulation of insect molding and metamorphosis, and the viral enzyme disrupts the hormonal balance of the insect host. It would be most interesting to characterize detoxifying enzymes among the currently over 50 *C. elegans* UDP-glycosyltransferases [2,3]. An interesting membrane-bound prokaryotic zeaxanthin glucosyltransferase has been characterized [9]. Even plant UDP-glycosyltransferases [3] may be functionally related to UGTs since they conjugate and store the same polyphenolic phytoalexins (Fig. 2) which were probably the driving force for evolution of multiple UGTs at the hepatogastrointestinal barrier in vertebrates. Of course, prokaryotic enzymes appear to be particularly interesting since they suggest the existence of sophisticated UGT-related UDP-glucosyltransferases already at the Precambrian/Cambrian border, over 500 million years ago when pro- and eukaryotic cells were developed and multicellular organisms had appeared [26].

6. Conclusions

Vertebrate UGTs represent major phase II enzymes of endo- and xenobiotic metabolisms leading mostly to detoxication and elimination of their substrates. Human UGT families 1 and 2 are the result of a long history, dating back to the evolution of fish species. Human UGT polymorphisms

show major differences in allelic frequencies among ethnic groups. Some of these allelic variants are important in predisposing individuals to abnormal drug reactions and toxin-mediated diseases. A major driving force for the evolution of multiple UGTs, and in particular of the UGT1 gene locus, may have been the struggle to detoxify dietary phenolic phytoalexins. In addition, 'animal–plant warfare' probably facilitated the evolution of adaptive co-regulatory mechanisms for the induction of UGTs with CYPs and other DMEs. A similar mechanism may have led to the evolution of related UDP-glucosyltransferases in insects and other invertebrates. Interestingly, plants stabilize and store the same polyphenolic phytoalexins which probably led to the evolution of UGTs at the hepatogastrointestinal barrier of vertebrates. Prokaryotic enzymes appear to be particularly interesting since they suggest the existence of sophisticated UDP-glucosyltransferases since the Precambrian/Cambrian border.

Acknowledgments

The author thanks Peter Mackenzie (Department of Clinical Pharmacology, Flinders University School of Medicine, Bedford Park, Australia) for valuable discussions and Christoph Köhle from the author's institute for graphical work.

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