Pharmacology & Therapeutics 134 (2012) 200–218

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate Editor: R. A. Prough

The glycosidation of xenobiotics and endogenous compounds: Versatility and redundancy in the UDP glycosyltransferase superfamily

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ARTICLE INFO

Keywords:
UDP glucuronosyltransferase
UDP glycosyltransferase
Glucuronide
Glycoside
UGT1
UGT2
UGT3
UGT8
Evolution and function

ABSTRACT

The covalent addition of sugars to small organic molecules is mediated by a superfamily of UDP glycosyltransferases (UGTs) found in animals, plants and bacteria. This superfamily evolved by gene duplication and divergence to manage exposure to a changing environment of lipophilic chemicals. The recent characterization of the UGT3A family provides further insights into the origin and evolution of this superfamily in mammals and the role of individual UGTs in the formation of the various chemical glycosides found in body tissues and fluids. Furthermore, the unique UDP-sugar specificities of the two enzymes in this family inform our knowledge of UGT structure relating to catalysis and UDP-sugar specificity. In addition to the UGT3 gene family, three other gene families, UGTs1, 2, and 8, are found in mammalian genomes. The 19 members of the UGT1 and 2 families have a major role in processing lipophilic chemicals due to their capacity to glucuronidate a broad range of structurally-dissimilar substrates. In contrast, the UGT3 enzymes only have a minor role, as their activities are very low in the major drug-metabolic organs, and their N-acetylglucosaminide and glucoside products are only a minor component of circulating and excreted drug metabolites. Although the endogenous role of the UGT3 family is still unknown, participation in the processing of lipophilic chemicals in specific cell types or at specific times during ontogeny cannot be excluded. In contrast to the UGT 1, 2 and 3 families, the single member of the UGT8 family appears to have no role in drug metabolism.

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Contents

1. Introduction

Our capacity to respond to drugs and organic chemicals present in the environment, and to regulate the milieu of chemical ligands in cells, is mediated by multigene families of drug metabolizing enzymes (Mackenzie et al., 2010). Although members of these families display regio- and stereo-selectivity towards chemicals, their broad, overlapping substrate selectivities ensure that few low molecular weight organic compounds escape metabolism. This plasticity is crucial to preventing chemical toxicity and controlling cellular homeostasis. One major family of drug metabolizing enzymes is the UDP

Abbreviations: CAPSL, calcyphosine-like; Cer, ceramide; CoA, coenzyme A; EGT, ecdysteroid glucosyltransferase; ER, endoplasmic reticulum; Gal, galactose; GalCer, galactosylceramides; GalNAc, N-acetylgalactosamine; Glc, Glucose; GlcCer, glucosylceramides; GlcNAc, N-acetylglucosamine; GlcUA, glucuronic acid; H3K4me3, histone H3 lysine 4 trimethylation; HLM, human liver microsomes; LMBRD2, limb region 1 domain containing-2; LdMNPV, Lymantria dispar nucleopolyhedrovirus; Man, mannose; 4-MU, 4-methylumbelliferone; MRP, multiple resistance protein; UDP, uridine diphosphate; UGCG, UDP-Glc:ceramide glucosyltransferase; UGT, UDP glycosyltransferase; UMP, uridine monophosphate; UTR, untranslated region; Xyl, xylose.

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0163-7258/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2012.01.009

glycosyltransferase (UGT) family[1] (Tukey & Strassburg, 2000; Miners et al., 2004; Mackenzie et al., 2005). Members of this family catalyze the covalent attachment of hexose moieties to lipophilic chemicals, thereby altering their biological properties and aiding in their recognition by influx and efflux transporters. The latter changes their distribution in the body and enhances their elimination via the bile or urine. This process of glycosidation[2] uses activated sugar donors in the form of the uridine diphosphate sugars, UDP-glucuronic acid (UDP-GlcUA), UDP-glucose (UDP-Glc), UDP-galactose (UDP-Gal), UDP-xylose (UDP-Xyl) and UDP-N-acetylglucosamine (UDP-GlcNAc), and hydroxyl, carboxyl, thiol, amine and carbonyl functional groups on the chemical as sugar acceptors. Glycosidation, in general, is a strategy for minimizing the accumulation of chemicals to toxic levels in cellular membranes by facilitating their excretion in urine and bile, and specifically, regulating intracellular concentrations of chemical signaling molecules (e.g. steroid hormones and other nuclear receptor ligands). In rare cases, glycosidation of small molecules may be an intermediate step in the synthesis of more complex cellular components, as illustrated by the formation of ceramide galactoside, an intermediate in sphingolipid synthesis (Bosio et al., 1996).

In mammals, the overwhelming role of glucuronidation in the metabolism of a vast array of environmental and dietary chemicals and endogenous products of metabolism, and the importance of the UGT1 and 2 families in this process is well documented (for example, see reviews of (Miners & Mackenzie, 1991; Mackenzie, 1995; Miners et al., 2004). In contrast, the role of glycosidation with other sugars including glucose, xylose, galactose and N-acetylglucosamine in mammals is much less understood. The focus of this review will be the newly discovered human UGT3 family. The members of this family have novel UDP-sugar specificities, however, their contribution to drug metabolism and endogenous metabolism remains largely unknown. This review will provide an overview of the importance of the UGT family from an evolutionary perspective, document the various chemical glycosides other than glucuronides found in human tissues and fluids, and discuss the role and importance of the UGT3A forms and other UGTs in their formation. This review will also describe current structural aspects of the UGT protein relating to catalysis and UDP-sugar specificity and suggest future studies to further clarify the physiological and toxicological roles of the UGT superfamily.

2. The UDP glycosyltransferase superfamily: gene structure and evolution.

The mammalian UGT superfamily comprises 4 families denoted UGT1, UGT2, UGT3 and UGT8; representatives of each of these 4 families can also be identified in many lower vertebrates. The UGT superfamily includes all glycosyltransferases that contain the UGT signature sequence (FVA)-(LIVMF)-(TS)-(HQ)-(SGAC)-G- X(2) -(STG)-X(2)- (DE)-X(6)-P-(LIVMFA)-(LIVMFA)-X(2)-P-(LMVFIQ)-X(2)- (DE)-Q, (X is any amino acid) (Mackenzie et al., 1997), and that conjugate sugars to small lipophilic chemicals, but not proteins, peptides, lipids or polysaccharides. Thus enzymes involved in the production of glycoproteins, glycolipids, or polysaccharides such as the glycosaminoglycans, are not included with the UGT superfamily. The exception to this is the UGT8 enzyme that, as discussed below, is involved in the production of glycosphingolipids.

2.1. UDP glycosyltransferase 1

2.1.1. Mammalian UDP glycosyltransferase 1 genes

The UGT1 genes are encoded by a single complex locus that is similarly arranged in all mammals examined thus far. In humans, the UGT1 locus spans approximately 200 kb on chromosome 2q37 and encodes 13 genes. Each gene has a unique promoter and first exon (exon 1), and shares a common set of four distal exons (exons 2–5) (Ritter et al., 1992; Gong et al., 2001). Transcription is initiated at each unique promoter, and the RNA product of the corresponding exon 1 is spliced to the shared exons 2–5. Thus each of the 13 transcripts has a unique 5′ portion and an identical 3′ portion; the latter is involved in recognition of the UDP-sugar.

The human UGT1 genes can be consolidated into 4 groups based on sequence similarity: UGT1A1, UGT1A6, the UGT1A2P–1A5 cluster, and the UGT1A7–1A13P cluster (Fig. 1). Exons 1A1 and 1A6 encode polypeptides that are approximately 50% identical; however, within the 1A2P–1A5 and 1A7–1A13P exon clusters; the encoded polypeptides are 75–92% identical. It has been proposed that this arrangement reflects evolution by two rounds of gene amplification and divergence: the first round of amplification generating four ancestral exons including 1A1, 1A6, proto-1A2P-5 and proto-1A7-13P; the second round expanding the 1A2P-5 and 1A7-13P clusters (Mackenzie et al., 2005). Four of the human first exons (1A2P, 1A11P, 1A12P and 1A13P) have been identified as pseudogenes because they contain mutations that would prevent their translation into functional proteins (Fig. 1).

The overall structural arrangement of the UGT1 cluster appears to be conserved in all mammals. The genomes of experimental model animals such as rat, mouse and rabbit contain clear orthologues of 1A1 and 1A6, and likely orthologues of several other exons as described previously (Mackenzie et al., 2005). Orthologous relationships are most clearly identifiable in human and non-human primate genomes. Indeed it has been observed that only two UGT1A genes vary between human and chimpanzee: UGT1A2 encodes a full length protein in chimpanzee while it is a pseudogene in humans, and UGT1A5 is a pseudogene in chimpanzee, while it encodes a full length and presumed functional protein in humans (Li & Wu, 2007).

The rat genome has ten exons 1, four of which are pseudoexons. The mouse locus contains eleven exons 1 including five pseudoexons and shows evidence of additional rounds of amplification and divergence leading to an additional functional 1A6-like exon and several additional 1A7-like pseudoexons (Zhang et al., 2004). This suggests ongoing dynamic evolution of the UGT1 locus with duplication/divergence events occurring as recently as the split between rat and mouse approximately 17 million years ago.

Adding to the complexity of the UGT1 locus, is the observation that an alternative form of the common exon 5 (called exon 5b) can be spliced into the human UGT1 transcripts, producing mRNAs that encode shorter variants of each UGT1 protein (Girard et al., 2007). The shorter proteins lack the transmembrane segment but retain the ability to localize to the endoplasmic reticulum and to bind to the co-substrate UDP-GlcUA. These short UGT1 forms are functionally inactive and can heterodimerize with full-length UGT1 forms and inhibit their activity (Bellemare et al., 2010). The short-form UGT1 proteins are widely distributed and expressed at significant levels in human tissues.

2.1.2. Other vertebrate UDP glycosyltransferase 1 genes

Chicken (*gallus gallus*), lizard (*Anolis carolinensis*), frog (*Xenopus tropicalis*) and zebrafish (*Danio rerio*) genomes contain Ugt1 clusters

[1] 'UGT' is commonly defined as 'UDP glucuronosyltransferase', as most scientific articles in the drug metabolism field deal with the UGT1 and UGT2 families, which use UDP-GlcUA as sugar donor. In this review, 'UGT' is used as the abbreviation for 'UDP glycosyltransferase' as recommended by the UGT Nomenclature Committee (Mackenzie et al., 2005). This enables reference to all members of the UGT family, including those that do not use UDP-GlcUA as sugar donor.

[2] 'Glycosidation' is any reaction that forms a glycoside. Hence, it refers to the generic process of attaching a hexose group in β-linkage to a small molecular weight compound to form a β-D-glycoside. If UDP glucuronic acid is used as sugar donor, the process is termed glucuronidation. Similarly, conjugation with glucose, galactose, xylose and N-acetylglucosamine is referred to as glucosidation, galactosidation, xylosidation and N-acetylglucosaminidation, respectively. In this review, the term 'glycosylation' will be used for the transfer of glycosyl groups to proteins or carbohydrate chains. However, in practice, 'glycosylation' and 'glycosidation' are used interchangeably.

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