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Commentary

From differential induction of UDP-glucuronosyltransferases in rat liver to characterization of responsible ligand-activated transcription factors, and their multilevel crosstalk in humans

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ABSTRACT

UDP-glucuronosyltransferases (UGTs) catalyze a major Phase II reaction in the endo- and xenobiotic-metabolizing enzyme (XME) system consisting of Phases I–III proteins and ligand-activated transcription factors. Differential induction of liver microsomal CYP activities following treatment of rats with aryl hydrocarbons or phenobarbital, discovered over 50 years ago, initiated studies to characterize multiple CYPs and the transcription factors Ah receptor (AhR) and CAR, respectively. Similar studies of UGT activities initiated studies of multiple UGTs. However, inducible human UGTs differed from those in rats. In addition, induction of UGTs is complicated, for example, by coordinate regulation of some XMEs by AhR and the antioxidant Nrf2 transcription factor. Functions of UGTs in the XME system are discussed using the following examples: (i) Tight coupling between Phase I and II enzymes in benzo[a]pyrene detoxification. In particular, AhR- and Nrf2-controlled quinone reductases and UGTs may prevent quinone–quinol redox cycling with generation of oxidative stress. (ii) CAR-mediated induction of UGT1A1 may be involved in perinatal detoxification of bilirubin neurotoxicity. (iii) PPARα-mediated glucuronidation of eicosanoids may contribute to their detoxification and homeostasis. Identification of the role of UGTs is challenged by intense crosstalk of transcription factors at the genetic level, the level of protein–protein interaction and control by signaling networks. Nevertheless, as drug targets ligand-activated transcription factors provide promising therapeutic possibilities.

1. Introduction

Differential induction of microsomal CYP activities by aryl hydrocarbons and phenobarbital was discovered over 50 years ago [1–4], and facilitated characterization of the CYP supergene family [5,6]. This discovery also stimulated identification of the responsible ligand-activated transcription factors (LATFs): AhR [7,8], CAR and PXR [9–11]. In addition, treatment of rats with fibrates led to their characterization as peroxisome proliferators [12], CYP4 family inducers [5], and identification of PPARα as the responsible LATF [13]. It was soon recognized that these inducers also differentially activated other xenobiotic-metabolizing enzymes (XMEs), for example, UGT supergene family members [14] which similar to CYPs are differentially induced in rat liver by aryl hydrocarbons, phenobarbital and fibrates [15–17]. Recognition of common LATF-binding response elements in the regulatory region of target genes suggests that Phases I and II XMEs, drug transporters (Phase III) as well as LATFs represent an evolutionary conserved detoxification system for lipid-soluble endo- and xenobiotics [5,11,18,19]. They are often functionalized in Phase I, conjugated in Phase II, and the water-soluble conjugates are exported from cells by transporters in Phase III. In addition, this system may also have evolved to regulate homeostasis of endobiotics [20] (Fig. 1). Phases I and II XMEs are also termed drug-metabolizing enzymes because of their importance for drug development and therapy.

The present commentary is focused on UGTs which exhibit a central role in the XME system, acting together with CYPs,and conjugate transporters. Control of CYP induction by LATFs has been covered in a number of elegant reviews [5,11,21,22]. Despite

Abbreviations: AhR, Ah receptor; BaP, benzo[a]pyrene; CAR, constitutive androstane receptor; CYP, cytochrome P450; GR, glucocorticoid receptor; GST, glutathione S-transferase; gtPBREM, glucuronyltransferase Phenobarbital-Responsive Enhancer Module; HETE, hydroxyeicosatetraenoic acid; LATFs, ligand-activated transcription factors; LTB4, leucotriene B4; Nrf2, nuclear erythroid-related factor 2; PB, phenobarbital; PXR, pregnane X receptor; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; UGT, UDP-glucuronosyltransferase; XME, xenobiotic-metabolizing enzyme.

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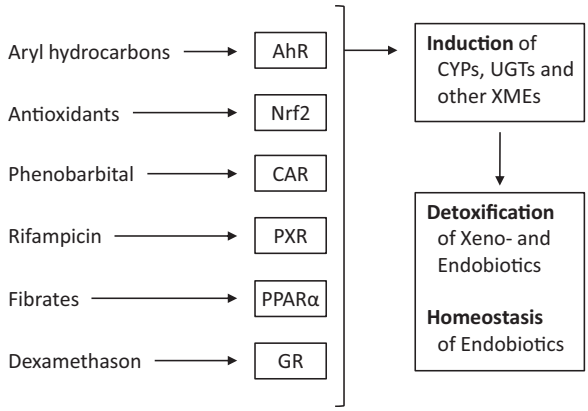

Fig. 1. From differential induction to identification of ligand-activated transcription factors regulating human hepatic CYPs, UGTs and other xenobiotic-metabolizing enzymes (XMEs).

common LATFs for different XMEs, special regulatory mechanisms have been recognized for Phase II enzymes such as UGTs and glutathione S-transferases (GSTs). For example, both AhR and the antioxidant Nrf2/Keap1 pathway are required for induction of UGTs. Recently, species differences in regulation of UGTs, and crosstalk between LATFs have become a major challenge. Therefore, the present commentary emphasizes regulation of human hepatic UGTs by LATFs and their multilevel crosstalk.

2. Overview of ligand-activated transcription factors (LATFs) responsible for induction of CYPs and UGTs

Ligand-activated transcription factors (LATFs) regulate hepatic XMEs in cooperation with liver-enriched transcription factors including HNF1, HNF4 and C/EBP [23–25]. Interestingly, when hepatic cell lines were supplemented with C/EBP-, HNF4α- and CAR-expressing vectors, expression of CYP2B6 and UGT1A1 was synergistically enhanced [26]. These findings underline the importance of cooperation between liver-enriched transcription factors and LATFs. LATFs responsible for induction of XMEs represent an interesting subgroup of transcription factors which acquired the ability to be modulated by small molecules in a manner similar to allosteric regulation of enzymes. Notably, the discussed LATFs are again under the control of higher order transcription factors. For example, the Wnt/β-catenin/TCF pathway may control both AhR and CAR. AhR and CAR expression are decreased in livers of ctnnb1-deficient male and female mice whereas PXR, PPARα and Nrf2 remained unaffected. Expectedly, expression of UGT1A6a and 1a6b was found to be decreased in these animals. The finding that AhR is a target of β-catenin signaling has also been reported by others (see [27] for references).

2.1. Ah receptor (AhR)

The AhR represents a multifunctional switch involved, for example, in metabolic adaptation, vascular development and dioxin-mediated toxicities [7]. In addition to xenobiotic aryl hydrocarbons and dioxins, a variety of endogenous ligands are presently discussed together with non-ligand activators [8]. Ligand-binding leads to nuclear translocation of the cytosolic AhR where it associates with its partner protein Arnt and binds to XREs (xenobiotic response elements) containing the core DNA sequence TnGCGTG. The first XRE was characterized in the promoter region of CYP1A1 [28]. In the case of UGTs, XREs were first identified in the regulatory region of rat liver UGT1A6 [29], human UGT1A6 [30,31] and human UGT1A1 [32]. In fact, all human UGT1 family members appear to be regulated by the AhR [33] in cooperation with subsequently discussed Nrf2.

2.2. Nrf2-Keap1 signaling

Treatment of rats with antioxidants/electrophiles leads to induction of Phase II enzymes and a battery of oxidative stress response genes [34–36]. In contrast, CYP1A1 was found to be downregulated by oxidative stress [37]. Search for the responsible transcription factor led to identification of Nrf2 [38–40]. Nrf2 is sequestered in the cytoplasm in complex with Keap1 (kelch-like ECH-associated protein 1). Nrf2 and Keap1 dissociate when Keap1 reacts with ROS (reactive oxygen species), other electrophiles and antioxidants. Thereafter, Nrf2 migrates to the nucleus where it associates with small Maf or related proteins and binds to AREs (antioxidant responsive elements) in target genes [40,41]. The first ARE was identified in the regulatory region of GSTA2 [41]. Nrf2-regulated genes such as UGT1A6 were identified using Nrf2-deficient and proficient mice induced by the selective Nrf2/Keap1 activator sulforaphane. Results of these studies suggested that glucuronidation and glutathione conjugation are 'more dependent on Nrf2-regulated genes than thought previously' [40]. Not only UGT1 and UGT2 genes but also UDP-glucose dehydrogenase (the enzyme generating the cofactor UDP-glucuronic acid) were found to be upregulated. Recently, it has been established that coordinate regulation of AhR and Nrf2 is required for induction of murine UGTs [42] and probably rat and human UGTs as well [31,43]. Roles of coordinate AhR and Nrf2 induction in detoxification and mechanisms of multilevel crosstalk are discussed in sections 4 and 5, respectively. Notably, Nrf2 is not a LATF: The protein interacting with electrophiles and ROS is Keap1. Release from binding to Keap1 leads to activation of Nrf2. However, due to necessary interaction between AhR and Nrf2 for induction of UGTs, Nrf2 is discussed here together with LATFs.

2.3. CAR and PXR

CAR (constitutive androstane receptor, NR1I3) and PXR (pregnane X receptor, NR1I2) are closely related, evolutionary-conserved xenobiotic sensors of the nuclear receptor superfamily [10,11,21]. They are discussed together since they share common activators and target genes. On the other hand, distinct activators and activation mechanisms are also known. For example, human PXR is selectively and directly activated by the antibiotic rifampicin; CAR is indirectly activated by phenobarbital-type inducers such as the antiepileptics phenobarbital, phenytoin and carbamazepine. The latter inducers do not bind to the CAR protein but trigger its nuclear translocation by a mechanism involving dephosphorylation of its threonine 38 [44]. However, how the cell recognizes phenobarbital-type inducers is still a mystery. Induction of UGTs by phenobarbital is known from early clinical studies. In fact, Crigler–Najjar syndromes I and II have been distinguished on the basis of phenobarbital induction of UGT1A1 [45]. CAR/RXR-binding domains were first identified in studies of UGT1A1 regulation [46,47], the only UGT responsible for bilirubin clearance in humans. Interestingly, the CAR-binding domain resides in a 290 base pair cluster, termed gtPBREM (glucuronosyltransferase Phenobarbital-Responsive Enhancer Module), discussed in Section 4.2. With regard to PXR it is known that this LATF transcriptionally activates a number of UGTs: UGT1A1 (in the gtPBREM cluster) [47] and also UGT1A3, 1A4 and 1A6 [24].

2.4. PPARα

Several evolutionary conserved PPAR isoforms have been identified. Here, the focus is on fibrate-activated hepatic PPARα

which controls mitochondrial and peroxisomal ß-oxidation of fatty acids [12,13]. Fatty acids and eicosanoids have been identified as potent endogenous ligands of PPARα [48,49]. For example, 8(S)-HETE has been demonstrated to be a high-affinity ligand with 100 nM half-maximal activity [48]. PPARα has been shown to be involved in all pleiotropic effects of peroxisome proliferators [50]. CYP4 family members were the first fibrate-induced XME target genes shown to be involved in omega-hydroxylation of fatty acids [5]. PPARα is involved in regulation of all phases of the XME system including regulation of many UGTs (UGT1A1, 1A3, 1A4 [51], 1A9 [52], 2B4 [53]). PPARα-induced hepatic UGTs are possibly involved in detoxification of eicosanoids, as discussed in Section 4.4.

3. Species differences of rat and human hepatic UGT induction by ligand-activated transcription factors (LATFs)

As discussed in the previous section, studies with LATF-deficient mice and with transgenic mice expressing human UGTs suggest that expression of UGTs is regulated by LATFs together with liver-enriched transcription factors. Notably, LATFs such as AhR are required to maintain both basal and ligand-induced UGT1A6 expression in mouse liver [54]. Species differences are expected since each species conceivably selects the regulatory conditions suitable for its ecological niche. As indicated in Table 1, differential induction of orthologous hepatic UGT1 members by AhR and CAR/PXR is obvious in rats but not in humans. In rat liver UGT1A6 is markedly induced by aryl hydrocarbons while UGT1A1 is not induced. In contrast, human UGT1A1 is induced by aryl hydrocarbons [33] while induction of UGT1A6 is low. Summing up all available information, induction of human UGTs is indicated by (+) in Table 1, despite <2-fold induction in some studies [55].

UGT2 members of different species cannot be compared since no orthologous UGT2 genes can be identified. Interestingly, expression of human hepatic UGT2 members (UGT2B4, 2B7, 2B10, 2B15 and 2B17) is in general higher than that of family 1 members [56,57]. UGT2 members are known to be involved in catabolism of steroids and bile acids. For example, UGT2B15 and 2B17 are strongly regulated by androgens [58]. Abundantly expressed UGT2B4 is regulated by bile acid-activated PPARα [52]. However, the contribution of UGTs in detoxification of steroids and bile acids is complex and beyond the scope of this commentary. The role of UGT2B4 in catabolism of eicosanoids is discussed in Section 4.4.

Human intestinal and hepatic UGTs are induced via AhR and Nrf2 by dietary phytochemicals [59], including unknown constituents of commonly consumed coffee [60]. Notably, the Nrf2 pathway induces both UGT1 and UGT2 family members. Nrf2-binding AREs have been identified in the promoter of UGT2B7 [61]. As discussed in Section 4.4, UGT2B7 is involved in detoxification of inflammatory eicosanoids such as HETEs and LTB4. Hence, Nrf2-mediated induction of UGTs may contribute to the hepatic antioxidant defense capacity which is possibly involved in prevention or amelioration of hepatitis [62,63].

Studies of human liver banks revealed large interindividual variation of UGT activities [56]. However, underlying factors (LATFs, liver-enriched transcription factors as well as genetic diversity [64]) are difficult to distinguish. In addition, recent evidence supports the concept that UGT proteins interact as dimers/oligomers which may have implications for structure, function and substrate specificity of UGTs [65]. Moreover, UGT activity may be controlled by regulated phosphorylation [66]. Despite these complexities, control of gene expression is important. It is proposed that it is mainly the concerted action of UGTs together with other members of the XME system which leads to effective detoxification, as indicated in the subsequent section.

4. Roles of UGTs in detoxification and homeostasis of xeno- and endobiotics

4.1. Roles of Phases I and II induction in detoxification of polycyclic aromatic hydrocarbons

Roles of CYP1A1 and CYP1B1 induction in bioactivation of carcinogenic polycyclic aromatic hydrocarbons such as benzo[a]-pyrene (BaP) have been well studied and controversially discussed. In particular, mouse lines deficient in one or another of the CYP1 genes have shown paradoxical effects [67]. When CYP1A1-deficient mice received BaP orally (125 mg/kg/day) all animals died within 30 days whereas all CYP1-induced wild-type mice survived, suggesting efficient BaP detoxification (rather than bioactivation) by the intestinal epithelium. In support of this interpretation, serum BaP was much higher in CYP1A1-deficient mice. Efficient detoxification has been proposed to be achieved by the degree of coupling between Phases I–III metabolism. BaP metabolism is complex leading, for example, (i) to BaP-7,8-dihydrodiol and BaP diol epoxides (the latter as ultimate genotoxic carcinogens) and (ii) to multiple BaP quinones as major cytotoxic tumor promoters/progressors ([59,68] for references). BaP quinones such as BaP-3,6-quinone have been identified as potent activators of AhR and Nrf2, the latter due to oxidative stress generated by quinone–semiquinone–quinol redox cycles [69]. Reductases such as NADPH-cytochrome P450 reductase reduce quinones by risky 1-electron pathways. However, there are

Table 1
Schematic representation of species differences of rat and human hepatic UGT regulation by ligand-activated transcription factors (LATFs). In contrast to the rat orthologous gene, human UGT1A7 is not expressed in liver but in the upper gastrointestinal tract. In addition to regulation by exogenous inducers, studies with LATF- and Nrf2-deficient mice suggest that basal expression of UGTs is also controlled by the discussed LATFs (indicated by +). Rat UGT induction data are taken from [17], human estimates are described in the text. (+) Indicates <2-fold, (++) 2–5-fold, (+++) >10-fold induction in livers of rats or in human primary hepatocyte cultures. n.d., not determined;0, no induction detectable; (–), rat UGT1A4 and UGT1A9 are pseudogenes.

Ligand-activated transcription factors (LATFs)	UGT1A family members					
	1	3	4	6	7	9
	(Induction factors)					
Rat:						
AhR	0	+	–	+++	+++	–
Nrf2	0	+	–	+	+	–
PXR/CAR	++	0	–	+	+	–
PPARα	+	+	–	0	0	–
Human:						
AhR	++	+	+	+	+	+
Nrf2	+	+	+	+	+	+
PXR/CAR	++	+	+	+	n.d.	+
PPARα	+	+	+	+	n.d.	+

also multiple Nrf2-inducible quinone reductases including NQO1 (NAD(P)H quinone reductase 1) which reduce quinones by 2-electron pathways whereby the toxic semiquinone step is bypassed. Efficient glucuronidation of the resulting quinols by coinduced UGT1A9 [70] (termed UGT1.7 in the early publication) may prevent oxidative stress. In support of oxidative stress as major trigger of the Nrf2 response, studies with NQO1-deficient Caco-2 cells led to induction of UGT1A6 by tert-butylhydroquinone whereas no induction was achieved in NQO1-proficient HT-29 cells [71]. In addition to oxidation to the diol epoxide, BaP-7,8-dihydrodiol may be converted to BaP-7,8-quinol by AKRs (aldoketo reductases) such as AKR1C1 which is AhR- and Nrf2 inducible [72]. The quinol is autoxidized to BaP-7,8-quinone and undergoes redox cycling with generation of oxidative stress [72]. The quinol may also be detoxified by UGTs and SULTs (sulfotransferases) but the responsible isoforms have not been identified. In conclusion, coordinate induction of AhR and Nrf2 gene batteries may be an example for detoxification of BaP by tight coupling between Phases I and II enzymes. Of course, the proposed roles of human AhR- and Nrf2-inducible UGTs in detoxification of carcinogenic polycyclic aromatic hydrocarbons need to be verified by epidemiologic studies using UGT polymorphisms, similar to the study of the role of UGT1A7 in smoking-related laryngeal cancer [73].

4.2. Perinatal UGT1A1 induction

Perinatal induction of UGTs by phenobarbital has been investigated for decades. Early studies suggested that 'late fetal and neonatal clusters' of inducible rat hepatic UGT activities [74] were identical to aryl hydrocarbon- and phenobarbital-inducible UGT activities, respectively [15,16]. Induction of UGTs from low fetal UGT activities to perinatal and adult values has been reviewed [56]. Low bilirubin UGT activity (in addition to hemolytic conditions) was found to be the major factor responsible for severe neonatal jaundice which is particularly frequent in preterm infants. Hyperbilirubinemia is neurotoxic in the neonate leading to brain damage, known as 'kernicterus' [75]. It is tempting to speculate that evolution of the gtPBREM cluster of binding sites for a number of LATFs in the promoter of UGT1A1 [46,47] may be related to the need for perinatal UGT1A1 induction in primates. This cluster contains binding sites for CAR and PXR [47], AhR [33], Nrf2 [76], PPARα [51] and for the glucocorticoid receptor [47]. It is obvious that perinatal induction represents a stressful condition. Glucocorticoids and other stimuli may activate their response elements in the gtPBREM of UGT1A1. Glucocorticoids have been demonstrated to induce CAR and PXR expression [22]. Hence, activation of different LATFs in the gtPBREM cluster depends upon the presence of activating ligands. Interestingly, the gtPBREM is perfectly conserved in the baboon [77]. It is localized at a similar distance to the transcription start site, and the sequence of cis-acting response elements for LATF-binding is highly conserved.

4.3. Possible autoregulatory control of UGT1A1 by bilirubin

Studies using CAR-defective mice demonstrated that all proteins involved in bilirubin clearance by hepatocytes are under the control of CAR including OATP1B1 and 1B3 (uptake transporters for bilirubin and bilirubin monoglucuronide into hepatocytes), GSTA1/2 (involved in intracellular binding of bilirubin), bilirubin conjugating UGT1A1 and Mrp2 (responsible for biliary secretion of bilirubin conjugates [78]. Low CAR expression in the fetus may contribute to neonatal jaundice [78]. Bilirubin is the toxic end product of heme catabolism. A significant amount of bilirubin is produced every day (250–400 mg in adult humans) which is cleared in the liver by the above CAR-regulated XME system. Interestingly, bilirubin is an activator of CAR [78] and of AhR ([8], for references). In support of the role of these LATFs in bilirubin catabolism, UGT1A1 has been demonstrated to be induced by aryl hydrocarbons and phenobarbital-type inducers in human primary hepatocyte cultures [79]. Bilirubin clearance is also enhanced by activators of PXR [80]. Hence, bilirubin-activated LATFs may provide an autoregulatory feedback loop which is not only operative in the stressful perinatal period but also in the adult.

In addition, the bilirubin-mediated autoregulatory feedback loop appears to be fine-tuned since bilirubin is not only neurotoxic in the neonate but also a powerful antioxidant [81,82]. The latter property may have facilitated the occurrence of a frequent polymorphism of UGT1A1, termed UGT1A1*28, responsible for Gilbert's syndrome. Homozygous expression of this allelic variant results in reduced expression of UGT1A1, moderately increased serum bilirubin, and may be responsible for reduced coronary disease in carriers of Gilbert's syndrome [83]. Interestingly, in the gtPBREM cluster a polymorphism (T3279G) was found in linkage disequilibrium with the UGT1A1*28 polymorphism which synergistically lowers UGT1A1 expression [84,85].

4.4. Control of eicosanoid catabolism by UGTs

Vasoactive and inflammatory eicosanoids activate LATFs and are detoxified by UGTs (Fig. 2). CYP4 family members are known to be involved in omega-hydroxylation of fatty acids, for example, human hepatic CYP4F3B is involved in omega oxidation of arachidonic acid to vasoactive 20-HETE (20-hydroxyeicosatetraenoic acid) [86]. 20-HETE is glucuronidated by several PPARα-induced UGTs, mainly by UGT2B7 [87]. It has been shown to be excreted in urine as 20-HETE glucuronide, particularly in liver cirrhosis [62,63]. In addition, arachidonic acid is oxidized by 5-LOX (5-lipoxygenase) to labile LTA4 which is converted either to vasoconstrictory LTC4 (leucotriene C4), or inflammatory LTB4, a known substrate of UGT2B7 [87,88]. Multiple HETEs have been characterized as PPARα agonists [11,48]. They are also substrates of UGT1A1, 1A3, 1A4, 1A6, 1A9 [51], and UGT2B4, 2B7 and 2B10 [87]. Interestingly, a stepwise increase in LOX metabolites such as 12- and 15-HETE characterizes the progression from normal liver to nonalcoholic fatty liver disease and steatohepatitis [63]. It is tempting to speculate that these UGTs may be involved in the prevention or attenuation of eicosanoid-mediated inflammatory responses in the initial stages of hepatitis. However, experimental approaches are needed to substantiate the role of UGTs in eicosanoid detoxification in vivo.

5. Multilevel crosstalk of LATFs controlling UGTs

Currently, crosstalk between LATFs and tissue-specific transcription factors in regulation of UGTs [24] and among LATFs

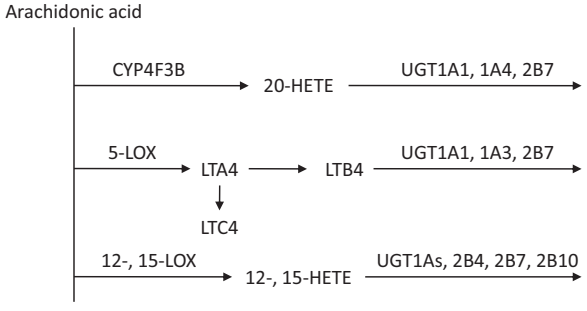

Fig. 2. Examples for possible feedback control between eicosanoid agonists of PPARα and their detoxification by hepatic UGTs. (a) CYP4F3B-generated vasocontrictory 20-HETE is a substrate of UGTs [88]. (b) 5-LOX-generated LTA4 is metabolized to inflammatory LTC4 (a metabolite of microsomal GSTs), and LTB4, a substrate of several UGTs [87]. (c) Several LOXs generate inflammatory HETEs which are substrates of indicated UGTs [87,88].

Table 2
Examples of multilevel crosstalk between UGT-controlling ligand-regulated transcription factors (LATFs). Details are discussed in the text.

Modes of crosstalk	Affected UGTs
(1) Genetic level	
AhR-Nrf2	Multiple UGT1 members [33,68,89,90]
AhR-CAR	UGT1A1 [93]
PXR-AhR	UGT1A1 [94]
(2) Protein–protein interaction	
AhR-Nrf2	Multiple UGT1 members [68,89,92]
GR-, CAR-GRIP1	UGT1A1 [96]
(3) Protein kinases/phosphatases	
CAR-MAP kinases via oncostatin M	UGT1A1 [98]

represents a major challenge which is just beginning to be understood. It occurs at multiple levels: at the genetic level or by recruitment of coregulators which again are embedded in signaling networks and epigenetic signatures. A few examples have been selected (Table 2).

5.1. AhR-Nrf2

Accumulating evidence in mice suggests that coordinate activation of AhR and Nrf2 may be required for induction of NQO1 as well as most GSTs and UGTs [42]. In support of these findings, experiments using AhR-deficient and -proficient rat hepatoma 5L cells suggest that AhR is necessary for induction by tert-butylhydroquinone, a prototypical activator of Nrf2-Keap1 signaling [31]. In humans, UGT1 members also appear to be regulated by both AhR and Nrf2 [43,89].

At the genetic level, Nrf2 has been found to be a target gene of AhR, based on functional XREs identified in the promoter of Nrf2 [90], On the other hand, AhR appears to be a target gene of Nrf2 [91]. However, coordinate induction of UGTs by AhR and Nrf2 may also be possible by direct or indirect (via coregulators) interaction between the two transcription factors, as discussed for the control of NQO1 [92]. Many questions remain: for example, does this AhR-Nrf2 crosstalk apply to all Nrf2-regulated genes? Do we have to distinguish regulation of Phase II XMEs from other antioxidant enzymes such as heme oxygenase 1, thioredoxin reductase, etc.? LATFs and functionally connected Nrf2 are multifunctional switches. Probably there is no clear distinction between their roles in regulating XMEs and other functions. Better knowledge about LATF-binding response elements of target genes may help to solve some of the problems.

5.2. AhR-nuclear receptor family members

CAR expression appears to be induced by TCDD via AhR in human liver [93], and some evidence for crosstalk between PXR and AhR has been obtained in human liver: rifampicin induces CYP1A1 and 1A2 via AhR in human primary hepatocyte cultures [94], although this finding remains complex and controversial [22]. PXR expression appears to be controlled by PPARα, based on PXR expression and PPREs in the promoter region of PXR [95].

5.3. Recruitment of coregulators

When LATFs bind to DNA, coregulators are recruited and corepressors are released. Coacticators are known to be involved in epigenetic chromatin remodeling, for example via histone acetyltransferases/deacetylases. In addition, mediator complexes are formed in multiple steps which are responsible for interaction of LATF complexes with the RNA polymerase II complex of the basal transcription machinery. A few examples of LATF coactivators controlling UGTs have been described. For example, CAR and GR synergistically crosstalk in UGT1A1 expression by recruitment of the coregulator GRIP1 (glucocorticoid receptor-interacting protein 1) [96]. Crosstalk between GR and CAR has been discussed in Section 4.2. It may be particularly important during perinatal adaptation to avoid bilirubin-mediated brain injury. Furthermore, CAR and PPARα transcription is only possible by interaction with the coregulator/mediator PBP/TRAP220: Conditional deletion of PBP/TRAP220 in hepatocytes abrogates all PPARα and CAR functions, i.e., phenotypes of PBP/TRAP-deficient mice are similar to those in mice lacking the respective receptor [97].

5.4. Control of ligand-activated transcription factors (LATFs) by protein kinases/phosphatases

Expectedly, LATFs are embedded in complex protein kinase/phosphatase signaling networks. The role of non-ligand activation of AhR has been critically discussed in [8]. As discussed before, phenobarbital-mediated nuclear translocation of CAR depends upon dephosphorylation of threonine 38 [44]. Studies using the Il-6-type cytokine oncostatin M provide an interesting example for LATF control by protein kinases. Oncostatin M binds to a plasma membrane receptor complex which, in contrast to other cytokines such as EGF, IL-1β and IL-6, positively enhances the CAR-UGT1A1 pathway via MAP kinase [98]. The cytokine is an important developmental factor of hepatocyte maturation and may contribute to perinatal induction of UGT1A1.

6. Conclusions

UDP-glucuronosyltransferases (UGTs) catalyze a major Phase II reaction in the endo- and xenobiotic-metabolizing enzyme (XME) system consisting of Phases I–III proteins and ligand-activated transcription factors (LATFs). LATFs represent an interesting subgroup of transcription factors which acquired the ability to be modulated by small molecules in a manner similar to allosteric regulation of enzymes. Differential induction of liver microsomal CYP activities following treatment of rats with aryl hydrocarbons or phenobarbital, discovered over 50 years ago, initiated studies on multiple CYPs and the responsible transcription factors, Ah receptor (AhR) and CAR, respectively. Similar studies of UGT activities initiated studies of multiple UGTs. However, inducible human UGTs differed from those in rats. For example, rat hepatic UGT1A6 is markedly induced by aryl hydrocarbons while rat UGT1A1 is not induced. In contrast, human UGT1A1 is induced by aryl hydrocarbons [79] while induction of human UGT1A6 is low. In addition, induction of UGTs is complicated by coordinate regulation of some XMEs by AhR and the antioxidant transcription factor Nrf2. Notably, Nrf2 is not a LATF. The protein interacting with endo- and xenobiotic electrophiles and ROS is Keap1, the cytosolic partner of Nrf2. Nevertheless, due to close coregulation of AhR and Nrf2 in the induction of UGTs (and of GSTs, NQO1 and AKR1C1) it may be justified to discuss Nrf2 together with LATFs.

Functions of UGTs in the XME system have been discussed using detoxification of aryl hydrocarbons such as benzo[a]pyrene, bilirubin and eicosanoids as examples. (i) Tight coupling between Phases I–III enzymes in benzo[a]pyrene (BaP) detoxification may explain in part paradoxical observations of AhR-mediated induction in cell cultures and in vivo. Whereas AhR-induced CYP1A1 is known to be responsible for BaP bioactivation in cell culture, CYP1A1-deficient mice were not protected against oral BaP exposure. In contrast, CYP1A1-inducible mice survived whereas CYP1A1-deficient mice died due to lack of intestinal first-pass BaP detoxification [67]. Tight coupling of Phases I–III may be

responsible for protection of the intestinal epithelium. In particular, AhR- and Nrf2-controlled quinone reductases and UGTs may prevent quinone–quinol redox cycling and subsequent generation of oxidative stress. Quinone reductases such as NQO1 reduce quinones by 2-electron reduction thereby bypassing the toxic semiquinone step; UGTs such as UGT1A9 have been shown to efficiently conjugate the resulting BaP quinols [70] which are rapidly exported by transporters. (ii) CAR-mediated induction of UGT1A1, the only human UGT responsible for bilirubin conjugation, may be involved in perinatal detoxification of bilirubin neurotoxicity. The perinatal induction of fetal UGT1A1 is an impressive adaptive process. It is proposed that the gtPBREM cluster (containing binding sites for AhR, Nrf2, CAR, PXR, PPARα and the glucocorticoid receptor) in the regulatory region of this enzyme is involved in this stress-mediated adaptation. In addition, bilirubin has been shown to activate AhR and CAR, in support of an autoregulatory loop. (iii) PPARα-mediated glucuronidation of eicosanoids may contribute to their detoxification and homeostasis. Vasoactive and inflammatory eicosanoids such as 20-HETE and LTB4 have been shown to be detoxified by UGTs, and these eicosanoids are agonists of PPARα.

Identification of the role of UGTs is challenged by intense crosstalk of transcription factors at the genetic level, the level of protein–protein interaction and control by signaling networks, as examplified by regulation of UGT1A1. Numerous epidemiologic studies have shown an association between reduced cancer risk and increased intake of phytochemicals present in vegetables and fruits. Consumption of phytochemicals including the common beverage coffee has been shown to induce UGTs. Hence, ligand-activated transcription factors as drug targets may provide promising therapeutic possibilities.

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