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Neonatal cytochrome P450 CYP3A7: A comprehensive review of its role in development, disease, and xenobiotic metabolism

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Abstract

The human cytochrome P450 CYP3A7, once thought to be an enzyme exclusive to fetal livers, has more recently been identified in neonates and developing infants as old as 24 months post-gestational age. CYP3A7 has been demonstrated to metabolize two endogenous compounds that are known to be important in the growth and development of the fetus and neonate, namely dehydroepiandrosterone sulfate (DHEA-S) and all-trans retinoic acid (atRA). In addition, it is also known to metabolize a variety of drugs and xenobiotics, albeit generally to a lesser extent relative to CYP3A4/5. CYP3A7 is an important component in the development and protection of the fetal liver and additionally plays a role in certain disease states, such as cancer and adrenal hyperplasia. Ultimately, a full understanding of the expression, regulation, and metabolic properties of CYP3A7 is needed to provide neonates with appropriate individualized pharmacotherapy. This article summarizes the current state of knowledge of CYP3A7, including its discovery, distribution, alleles, RNA splicing, expression and regulation, metabolic properties, substrates, and inhibitors.

1. Introduction

The human cytochrome P450s (CYP450s) consist of a superfamily of heme-thiolate monooxygenases that metabolize a diverse array of exogenous and endogenous substrates, including hormones, drugs, toxins, and certain fatty acids [1-3]. The CYP3A subfamily is a major subfamily of human CYP P450, representing approximately 30% of all hepatic cytochrome P450 content, and it is involved in the metabolism of most drugs used clinically [1,4-6]. The human CYP3A subfamily is constituted of four functional isoforms: CYP3A4 [7,8], CYP3A5 [9,10], CYP3A7 [11,12], and CYP3A43 [13,14], as well as three CYP3A pseudogenes [15,16].

In adults, CYP3A4 is the predominant CYP3A isoform, accounting for 10–50% of total hepatic CYP, and metabolism of nearly 50% of currently administered drugs [5,17]. While

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Appendix A. Supplementary data

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CYP3A5 and CYP3A43 are primarily extrahepatic enzymes, they also exist in the liver, but at lower levels (10–30% of total CYP content) [10,18] and only 0.2–5% [16] that of CYP3A4, respectively.

CYP3A7 is found predominantly in human fetal livers and presents in embryonic hepatic tissues as early as 50–60 days of gestation [11,19-22], accounting for up to 50% of the total fetal hepatic CYP content and up to 87–100% of total fetal hepatic CYP3A content [23-26]. However, its expression has also been reported in other fetal tissue types, including the adrenal gland, kidney and lung [27]. When originally described by Kitada and Kanakubo [11], CYP3A7 was thought to be an exclusively fetal enzyme. Yet, more recent studies with neonatal and pediatric livers have identified significant levels of CYP3A7 up to 24 months post-gestational age [23,26,28,29]. Unique for any known human cytochrome P450, CYP3A7 begins to gradually decrease during the third trimester of pregnancy but remains active in many individuals during the first year of life, concomitant with gradual increases in CYP3A4 beginning after birth [23,26,28,30,31]. That is, CYP3A7 and CYP3A4 appear to exhibit a mirror image pattern of expression, with CYP3A7 levels declining after birth even as CYP3A4 levels increase.

This isoform switching phenomenon has profound implications for drug and xenobiotic metabolism in the neonate and developing infant. This is due to the fact that, while CYP3A4 and CYP3A7 share 87% amino acid sequence identity [12,32], and a wide overlapping substrate range [33], CYP3A7 is known to be substantially less catalytically active and can generate an altered profile of regiospecificity compared with CYP3A4/5 [29,33,34]. These differences in metabolism can lead to profound differences in drug efficacy and toxicity in the neonate and developing infant [29,35-37].

Interestingly, CYP3A7 expression has also been reported in a minority of adult human livers, human placenta, endometrium [38,39], and hepatocarcinoma [40], indicating that its presence is not exclusive to either the fetus or the developing infant. Furthermore, an allelic variant with a mutation in the promoter region, known as *CYP3A7*1C*, occurs with 5% frequency in the population and can lead to high levels of expression of the enzyme well into adulthood [31,37,40]. While it is unclear what role CYP3A7 plays in adult extrahepatic tissue, given its established biological importance in the infant, this may be an active area of future study.

Because CYP3A7 mediates the biotransformation of a wide variety of exogenous and endogenous compounds and is involved in the safety and efficacy of a number of drugs, as well as certain disease states in the adult, there has been increased interest in its biological role(s) in humans. In order to provide insight on our current level of understanding of this important CYP enzyme, this review summarizes the available knowledge on the biological role, substrates, inhibitors, activators, expression and regulation patterns, and general relevance to disease, of human CYP3A7.

2. Discovery

At least since the early 1970's it has been known that human fetal liver had the capacity to metabolize many xenobiotic compounds, even at early stages of gestation [41]. Additionally, Cresteil et al. observed that fetal livers exhibited higher dehydroepiandrosterone (DHEA) 16α-hydroxylase activity than adult livers [42]. In the fetus and developing infant, DHEA is a hormone that functions as a precursor for androgens and estrogens that are important for growth and development.

Subsequent to these initial observations, a CYP isoform, originally referred to as P450 HFLalpha, was isolated from fetal livers [11,27], and found to be the major enzyme responsible for the 16α-hydroxylation of DHEA sulfate (DHEA-S), the storage form of DHEA [43]. This enzyme was later designated CYP3A7 [44]. In 1989, the entire CYP3A7 cDNA was cloned from a fetal library [12]. CYP3A7 was found to share 95% nucleotide identity and 87% amino acid identity with CYP3A4, suggesting that the two isozymes might share an overlapping substrate range [45].

3. Gene location

CYP3A7 and the other CYP3A genes form a gene cluster which is in the order of 3A43, 3A4, 3A7 and 3A5 on chromosome 7q21-q22.1. In the intergenic regions, several additional cytochrome CYP3A exons form three pseudogenes (CYP3APs) (Fig. 1A) [15,16,46].

4. Distribution

CYP3A7 protein is mainly expressed in fetal livers with much lower levels in extrahepatic tissues including kidney, lung, stomach, intestine, adrenal, thymus, placenta, Jejunum and prostate [39,47-54]. However, the data on CYP3A7 expression in kidney, endometrium, and lung are somewhat conflicting. Haehner et al. (1996) found CYP3A7 mRNA in only one out of 25 kidneys [18], and Koch et al. (2002) described only a marginal expression of CYP3A7 in the kidney [50]. Conversely, Murray and colleagues detected CYP3A7 transcripts in all kidneys they investigated [52]. Also, while Schuetz et al. [39] and Sarkar et al. [55] found that CYP3A7 was expressed in the endometrium; Hukkanen et al. [56] and Williams et al. [57] did not detect it there. Finally, Anttila et al. [58] could not detect CYP3A7 mRNA in lung samples, but Kivisto et al. could [59]. Many of these studies illustrate the difficultly of trying to immunochemically detect CYP3A7 with a less than specific CYP3A antibody [31,60]. This has been an issue that has stymied quantification of CYP3A7 in fetal tissues for some time. However, newer proteomic based methods have recently shown promise [29] and some of the previous studies may be revisited with these newer methods in the future. In any case, it seems likely that the fetal liver remains the main location of CYP3A7 expression in the fetus and neonate.

5. Substrates of CYP3A7

5.1. Typical substrates

As mentioned in the introduction, CYP3A7 metabolizes numerous exogenous and endogenous compounds (Table 1).

In many cases, CYP3A7 has similar characteristics to CYP3A4 and CYP3A5 regarding substrate specificity, regiospecificity, and K_m; likely due to the high similarity in their overall structures (there are only 56 individual amino acid differences between CYP3A4 and CYP3A7). However, as described by Williams et al. (2002), the catalytic efficiency of the enzyme is generally greatly diminished for the turnover of most substrates when compared with CYP3A4/5 [33]. It is worth noting that CYP3A7 exhibits a striking catalytic preference for at least two substrates: DHEA-S and all-trans retinoic acid (atRA), with higher catalytic efficiency for both over CYP3A4/5, suggesting an important evolutionary role for this enzyme in the oxidation of these two hormones that are important in growth and development [28,68,83]. Additionally, other studies have demonstrated that CYP3A7 shows a preference in oxidation of 16α-hydroxylation activity of estrone over 2-hydroxylation, but no oxidation product preference for 17β-estradiol [64]. However, for the remaining substrates held in common, CYP3A7 generally exerts much less catalytic efficacy than CYP3A4/5 (Table 1).

5.1.1. DHEA—CYP3A7 converts DHEA-S and DHEA to the major metabolite 16α-OH DHEA-(S) [28,68] and minor metabolite 7β-OH DHEA-(S) [28], respectively. In contrast, 7β-hydroxylation of DHEA-(S) is the preferred reaction for CYP3A4 and 7β-OH DHEA-(S) is the major metabolite [28,30,43]. Based on the catalytic differences in DHEA-S oxidation by both enzymes, DHEA has been applied to differentiate the developmental expression of human hepatic CYP3A isoforms. For exclusively fetal liver samples, the CYP3A7 protein level correlated directly with DHEA 16α-hydroxylase activity due to the negligible presence of CYP3A4 enzymatic activity [28]. For differentiation of CYP3A4 and CYP3A7 in postnatal samples, although the amount of 16α-OH DHEA formed by CYP3A4 is relatively low, it is sufficient to impact CYP3A7 enzymatic activity assays used to determine the amount of CYP3A7 content [28,84]. Stevens et al. developed a DHEA 16α-/7β-metabolite profile-based multivariate regression model to simultaneously calculate CYP3A4 and CYP3A7 protein present in an individual liver [28]. The validity of this novel indirect approach was assayed by using both fetal and postnatal liver samples and indicated some promise in estimating CYP3A7 activity [28,31].

5.1.2. All-trans-retinoic acid—CYP3A7 metabolizes all-trans-retinoic acid (atRA) to 4-OH-, 18-OH-, 4-oxo- and 5,6-epoxy-RA, with 4-OH-RA being the major metabolite. Conversely, the contribution of CYP3A4 to the formation of 4-OH-, 18-OH-, and 4-oxo-RA is regarded to be minimal [62,83]. In particular, atRA metabolism by hepatic CYPs demonstrated that CYP3A4 could not catalyze the conversion of atRA to 18-OH- or 4-oxo-RA when the atRA concentration was below 50 μM, whereas the formation of these two metabolites was preferentially catalyzed by CYP3A7 at these concentrations [83], implying that atRA 4-OH, 18-OH, 4-oxo may have potential as *in vivo* CYP3A7 biomarkers. More

recently, Topletz and colleagues (2019) have shown that while CYP3A7 is the predominant CYP responsible for clearance of atRA in the fetal liver, it does not contribute substantially to clearance of maternal atRA during pregnancy [85]. Given this evidence, CYP3A7 is not likely to provide a sufficient maternal-fetal barrier for atRA exposure during fetal development, suggesting that regulation of total atRA exposure of the fetus is controlled by other mechanisms.

5.1.3. Testosterone—In the adult, CYP3A4/5 are the CYPs responsible for the formation of 6β-OH testosterone from testosterone [30,68]. In contrast, in the fetus, neonate, and developing infant, 2α-OH testosterone is the major testosterone metabolite produced by CYP3A7, the most abundant CYP3A isoform in these individuals [33,34,60], while CYP3A4/5 contribute only minimally to the formation of 2α-OH testosterone in the adult. As noted by originally by Leeder et al. (2005) and more recently by Kandel et al. (2017), there exists a strong divergence in the ratio of 2α-/6β hydroxylation activities between the three CYP3A isoforms (CYP3A7, 1.19; CYP3A5, 0.079; CYP3A4, 0.007), that is, the ratio of 2α-/6β-OH activities of CYP3A7 was one order of magnitude greater than CYP3A5, and two orders of magnitude greater than CYP3A4 [34,60]. The variation of this ratio between CYP3A7 and other CYP3A isoforms originally suggested that it may be a unique endogenous biomarker for discriminating CYP3A isoform activity or identifying CYP3A7 [60]. However, more recently, Kandel et al. (2017) observed that the 2α-/6β-OH ratio varied with testosterone concentration, suggesting that the correlation between the 2α-/6β-OH ratio and CYP3A7 activity may be weak in individuals with higher levels of testosterone [34].

5.1.4. Imipramine—Imipramine is a tricyclic antidepressant and its N-demethylation product has been employed as probe for CYP3A7 activity. However, a complicating factor is that in addition to CYP3A7 other CYP isoforms, particularly CYP1A2 and CYP3A4, also contribute significantly to the metabolic N-demethylation reaction [86]. In an attempt to resolve this, selective inhibitors have been used to exclude imipramine N-demethylation enzymatic activity due to CYP isoforms other than CYP3A7 [19]. In fetal liver, CYP3A7 is the dominant CYP3A isoform and CYP3A4/5 levels are negligible to non-existent [28,31], and therefore a limited number of isoform specific inhibitors is required. Using imipramine as the probe substrate, Chen et al. confirmed that CYP3A7 is the major CYP isoform in human prenatal hepatic tissues [19]. However, it seems that imipramine may not be an ideal probe in analyzing postnatal liver samples due to the confounding effects from other CYP isoforms capable of carrying out the N-demethylation reaction.

5.2. Absolute CYP3A7 quantification and the search for (potential) biomarker substrates

Commercial polyclonal antibodies raised against a CYP3A5 peptide or a CYP3A4 peptide (recognizing both CYP3A4 and CYP3A7) are available. However, while CYP3A5 protein expression can be distinguished from CYP3A7 by immunoquantitation based on Western blot, no effective immunological approaches have been developed for discriminating between CYP3A4 and CYP3A7 due to the lack of availability of isoform-specific antibodies, as noted above. Additionally, exclusive marker enzyme activities or specific inhibitors still do not exist for CYP3A7 as of our writing [28]. In this light, the routine assessment of CYP3A7 concentration in fetal human liver microsomes (fHLMs) and post-

natal human liver microsomes (HLMs) using proteomics methods holds great promise [29]. This, combined with approaches to measure the specific enzymatic activity of CYP3A7 in HLMs could help improve the predictivity of neonatal and pediatric pharmacokinetic models of drug disposition. However, for this to be the case, endogenous biomarkers of CYP3A7 activity need to be established and validated. In furtherance of this goal, approximative approaches based on the combination of substrate regioselectivity of the isoforms with other associated strategies have been reported and may yet prove of some value [28]. In conjunction with multivariate regression model or inhibitors, DHEA-S 16α-hydroxylation, testosterone 6β-hydroxylation, and testosterone 2α-hydroxylation have all been used as marker reactions in an attempt to identify the catalytic activity of CYP3A7 (Table 2), as discussed above.

6. Inhibitors/activators of enzymatic activity of CYP3A7

Discovery of an isoform-specific inhibitor is vital for identifying CYP3A7 activity *in vivo* and elucidating its catalytic mechanism. An additional aspect that makes the study of CYP3A7 inhibitors attractive is that both endogenous and xenobiotic inhibitors could be involved in the regulation of CYP3A7 metabolism *in vivo*. To date, although a variety of CYP3A7 inhibitors (many of which are drugs) have been reported (Table 3), important parameters such as the type of inhibition and specificity of isoform interaction need further investigation to find a CYP3A7-specific inhibitor. In a recent publication, Godamudunage et al. examined the differential inhibition and binding affinity between CYP3A7 and CYP3A4 for thirteen different azole antifungal compounds, several of which are commonly prescribed in the neonatal intensive care unit [87]. The authors observed that all the imidazole-containing azoles bound to both enzymes via a typical type II coordination to the heme iron. Additionally, they were found to inhibit both enzymes with IC50 values ranging from 180 nM for clotrimazole, the most potent inhibitor, up to the millimolar range for imidazole. For most of the azoles tested, CYP3A4 was inhibited more strongly than CYP3A7, with clotrimazole being the least selective inhibitor examined (less than 1.5-fold), and econazole the most selective (more than 12-fold). Of the 1,2,4-triazole-containing azoles examined in this study, only posaconazole inhibited CYP3A7, again less potently than CYP3A4. In general, the same azole compounds were observed to inhibit both enzymes, albeit more weakly with CYP3A7 than with CYP3A4 [87]. Given the results of this study, and the other information available in the literature, it is clear that the inhibition profile of CYP3A7 is highly similar to that of CYP3A4/5, certainly making finding an isoform specific inhibitor a difficult task for the foreseeable future.

In contrast, several compounds enhancing CYP3A7 enzyme activities have also been reported. This is perhaps not surprising, given the well-known and long described nature of allosteric enzyme activation in the CYP3A family [93-97].

While not tested against an exhaustive set of substrates, these compounds were found to activate at least two reactions, that is: 10,11-epoxidation of carbamazepine and O-dealkylation of 7-benzyloxy-4-trifluoromethylcoumarin (Table 4).

It should be recognized that, in at least a few cases, a molecule can act either as an inhibitor or activator, depending on the substrates and reactions considered. For instance, α-naphthoflavone inhibited CYP3A7-dependent imipramine demethylation [19] while activating CYP3A7-mediated 7-benzyloxy-4-trifluoromethylcoumarin metabolism [92]. This curious type of behavior is likely due to the nature of the multiple ligand binding sites within the CYP3A7 active site cavity, as has been demonstrated for CYP3A4 [98-100].

7. Inducers/suppressors of the expression of CYP3A7

Expression of CYP3A7 can be induced or inhibited in response to the presence of various compounds, thereby affecting the catalytic activities of CYP3A7 in the liver at any particular point in time. The reported inducers/suppressors of CYP3A7 are summarized in Table 5. Interestingly, the majority of compounds described in the literature tend to have the effect of increasing the expression of the CYP3A7 gene. Some natural products can also exhibit either induction or suppression of the CYP3A7 gene. For instance, apple polyphenols upregulated, whereas St. John's wort downregulated, the expression of CYP3A7 [101,102] (Table 5).

8. Physiological roles

8.1. Relevance to development and fetal protection

CYP3A7 catalyzes numerous reactions involving both xenobiotic and endogenous substrates and hence has potential roles in both protecting the fetus from exposure to drugs and maintaining the balance of various steroid hormones [62,119].

In regards to its role in regulating endogenous steroids, it has been known for some time that excessive DHEA-S is involved in intrauterine growth retardation, which often leads to premature birth [120,121]. Since CYP3A7 has a high catalytic activity for the 16α-hydroxylation of DHEA-S [43,64,84], it can protect the fetus from the buildup of toxic levels of this steroid and prolong the fetal maturation process. CYP3A7 also participates in the synthesis of estrogen, a primary female hormone during pregnancy, that requires oxidized DHEA-S as a precursor [122]. Through adjustment of CYP3A7 enzymatic activity, the fetus can regulate the placental production of estradiol from DHEA-S in order to protect it from exposure to excessive estradiol during development [123]. Consistent with this, DHEA-S and other sulfate conjugated steroids have been reported to activate the catalytic activity of CYP3A7, but not CYP3A4 [32]. Therefore, in general, elevating CYP3A7 activity provides a protection against hyperestrogenization by 16α-hydroxylation of estrogen precursors and estrogens themselves [124]. As a corollary, it follows that changes in the expression and activity of CYP3A7 in utero may have a profound influence on steroid biosynthesis, thereby affecting normal fetal development and the maintenance of pregnancy.

Similarly, inhibition of CYP3A7's role in atRA metabolism can have drastic effects on the fetus since atRA is essential for normal human growth and development. Both excessive and insufficient atRA can lead to birth defects. Indeed, excessive atRA in particular has be demonstrated to exhibit potent embryotoxicity and teratogenicity [125,126]. CYP3A7 catalyzes atRA to form several much less toxic hydroxylated metabolites, including the

major metabolite 4-OH-tRA. In this regard, CYP3A7 has important implications in protecting the fetus against atRA-induced embryotoxicity and teratogenicity and, therefore, interference in this function can have profoundly negative consequences on the fetus, up to and including premature termination of the pregnancy [62].

8.2. CYP3A7 interaction with environmental xenobiotics

Given its important role in the metabolism of endogenous hormones that are essential for fetal growth and development, and the promiscuous nature of the CYP3A family, it should come as no surprise that many environmental xenobiotics can have deleterious effects on the metabolism of these same CYP3A7 substrates. In a seminal study on the effects of insecticides on fetal development, Caron-Beaudoin et al. used a unique co-culture model of fetoplacental steroidogenesis and found that metabolism of neonicotinoids (thiacloprid, thiamethoxam and imidacloprid) by CYP3A7 impeded DHEA-S 16α-hydroxylation, which is normally transformed into estriol by placental aromatase, thereby presenting risks for normal fetal development in pregnant mothers that might have been exposed to excessive amounts of these pesticides [112].

Likewise, other work has demonstrated that certain environmental pollutants, such as procarcinogens, can also be metabolically activated by CYP3A7. Many carcinogens exhibit their corresponding toxic roles via bioactivation conducted by biotransformation enzymes, particularly CYPs. For example, aflatoxin B1 (AFB1) exerted its carcinogenic toxicity after being metabolized to the reactive AFB1-8,9-exoepoxide [127,128]. In the fetus, CYP3A7 was found to be predominantly responsible for the bioactivation of some carcinogens such as AFB1, sterigmatocystin, and AFG [129-133]. Additionally, the overexpression of human CYP3A7 has been observed to increase aflatoxin-induced mutations in murine models [134]. When taking these data into account, Wells et al. postulated that the high expression of CYP3A7 in fetal livers, coupled with a low capacity in detoxification of AFB1, could result in a high risk for a fetus via transplacental exposure [135].

8.3. Relevance to disease

CYP3A7 has also been reported to be associated with several disease states, including congenital adrenal hyperplasia [136], chronic lymphocytic leukemia, both breast and lung cancer [137], ovarian endometriosis [138], polycystic ovary syndrome [139], respiratory distress syndrome [140], congenital anomalies [60], endometrial cancer [141], and end-stage liver diseases [142], primarily ascribed to the phenotypic modulation of DHEA-S levels by *CYP3A7* variant alleles (especially *CYP3A7*1C*).

In contrast, although the *CYP3A7*1C* allele was associated with decreased bone mass at the lumbar spine in postmenopausal women, no direct association was found between *CYP3A7*1C* and serum DHEA-S levels, implying this genetic variation might influence bone mass via other CYP3A7 hormonal substrates known to protect bone [143]. Gender may play a role in the relationship between the *CYP3A7*1C* polymorphism and serum DHEAS level. In line with Bacsi et al., Smit et al. found that in a separate analysis for females no statistically significant difference was reached, although *CYP3A7*1C* was associated with lower serum DHEA-S levels in the whole cohort overall [143,144]. In addition, females

showed significantly lower DHEA-S levels than males regardless of wild type or *CYP3A7*1C* variant [144]. The gender differences in the association between CYP3A7 expression and DHEA-S levels suggests that the impact of CYP3A7 mutations on serum DHEA-S levels is stronger in males than in females, for as yet unknown reasons [143].

Genetic variation in CYP3A7 has also been described to be involved in daily drug dose requirements as well as having a profound effect on levels of endogenous hormones [77,136,145,146]. *CYP3A7*1C* carriers required a 1.4- to 1.6-fold higher cyclosporine daily dose during the first year after transplantation in a group of Caucasian renal or lung transplant recipients, due to increased cyclosporine metabolism [77]. In another study, the *CYP3A7*1C* carriers required a significantly decreased glucocorticoid dose ascribable to *CYP3A7*1C* lowering androgen levels [136].

In adults harboring the *CYP3A7*1C* allele, *CYP3A7* could be responsible for up to 80% of the total biotransformation of retinoic acid [47] and, therefore, in these individuals hepatic CYP3A7 expression could be a determinant for the outcome of retinoic acid therapy. In premenopausal women, *CYP3A7*1C* is associated with lower urinary estrone levels, and thus may be related to increased breast cancer risk [146,147]. Finally, *CYP3A7*1C* expression in a cohort of adult women has also recently been ascribed to increase the risk of birth control hormone failure due to increased hormone metabolism [148].

9. Genetic regulation of CYP3A7 expression

The enzymatic activity of CYP3A7 is developmentally differential with high variability among individuals, and most of this variability has been attributed to genetic factors [46,53,144]. The regulation of *CYP3A7* has turned out to be quite complex and involves a number of genetic control elements. Indeed, Sp1, Sp3, HNF-3β, USF1, XREM, and NFκB have all been implicated in regulation of the CYP3A7 gene [149,150].

9.1. Variant alleles

Several variant alleles of the *CYP3A7* gene have been identified, including 2 coding region and 4 noncoding region variants (Table 6).

Most of these variants appear as heterozygous with the wild-type allele and some of them have been associated with altered drug clearance and response and disease susceptibility [47,77,136,142]. The most frequent allele, *CYP3A7*2*, is caused by C > G transversion in exon 11 which results in the replacement of Thr409 with Arg, with highly variable interethnic occurrence frequencies varying from approximately 8% in Caucasians to 62% in Tanzanians. The frequency of *CYP3A7*2* in Asians was found to be 26–28% [53,153]; statistically higher than in Caucasians, but lower than that in Tanzanians. From the data acquired to date, it appears that the *CYP3A7*2* allele is the only allele that occurs more frequently than the wild-type, but this has only been found to be the case in the Tanzanian population [53]. In HEK293 cells, there were no significant discrepancies in expression levels between CYP3A7.1 and CYP3A7.2. Fetal livers homozygous for *CYP3A7**2 had similar or higher CYP3A7 protein contents than *CYP3A7*1* carriers. CYP3A7.2 was found to be more active in the metabolism of DHEA, luciferin BE, and alprazolam [53]. In

contrast, Leeder et al. did not see significant differences in DHEA metabolism between *CYP3A7*1* and *CYP3A7*2* using fetal liver microsomes [60]. Differences in ethnicity, sample size and analytical methods may have led to this discrepancy between the two studies. Because *CYP3A7*2* possibly leads to higher enzymatic activity, ethnic differences in CYP3A7-mediated fetal drug metabolism or detoxification merit further study.

The *CYP3A7*3* allele is derived from a thymidine insertion (4011insT) in exon 2 of *CYP3A7*, leading to a truncated CYP3A7 protein at the 55th residue, thus possibly producing a null phenotype. The *CYP3A7*3* allele seems to only occur in Korean subjects, and with a very low frequency (0.21%). No reports have linked *CYP3A7*3* with alterations in CYP3A7 expression or catalytic activity [153]. The rarity in loss-of-function mutations demonstrates the functional conservation and crucial role that CYP3A7 plays in the developing fetus.

None of the variant alleles with SNPs in the coding regions of CYP3A7 described thus far have accounted for the extent of observed variability in expression [158]. These coding variants may contribute to but are not likely to be a major driver of the inter-individual differences observed in CYP3A7 expression and/or catalytic activity.

The *CYP3A7*1B* allele has frequencies of 1% in Caucasians and < 1% in other ethnic groups (Table 6) [47,151,152]. Although less frequent, *CYP3A7*1B* was associated with increased *CYP3A7* expression in livers, but the mechanism of action is at present unknown [47].

The *CYP3A7*1C* allele occurs in the proximal promoter of *CYP3A7* through replacing an approximately 60-bp stretch (−127/−186) of the *CYP3A7* promoter with the corresponding region in *CYP3A4* [152]. The *CYP3A7*1C* allele thus possesses the transcription binding site CYP3A4-ER6 which has a higher affinity for PXR and CAR, resulting in a significant expression of CYP3A7 well into adulthood [47]. In general, *CYP3A7*1C* allele frequencies range from approximately 1.7%–6% depending on the ethnic group being considered (Table 6). Interestingly, *CYP3A7*1C* was not found to occur in Koreans [153].

CYP3A7 has been shown to be expressed in more than 10% of adult livers and intestines [47,50,115,152,156,159]. However, not all of these individuals expressing *CYP3A7* carry the *CYP3A7*1C* allele [47,152,156]. Meanwhile, some *CYP3A7*1C* carriers exhibited no *CYP3A7* expression at all [152,156]. These data imply that *CYP3A7*1C* carriage is neither necessary nor sufficient for the expression of CYP3A7 in adult livers.

*CYP3A7*1D* is a rare variant with allele frequencies similar to those of *CYP3A7*1B* (1%≤). Unlike *CYP3A7*1C, CYP3A7*1D* was not associated with high CYP3A7 expression in adults [47]. No further information on *CYP3A7*1D* is available at present.

*CYP3A7*1E* showed the highest allele frequency in African Americans (8%). Although Leeder et al. found one Caucasian sample was heterozygous for the *CYP3A7*1E* allele, Kuehl et al. and Lee et al. did not detect the *CYP3A7*1E* allele in Caucasians [60,152,153]. No apparent relationship existed between *CYP3A7*1E* and DHEA16α-OH activity [60].

However, neonatal *CYP3A7*1E* resulted in higher rate of respiratory distress syndrome [140].

9.2. RNA splicing

A pseudogene, *CYP3AP1*, is located between *CYP3A7* and *CYP3A5* (Fig. 1A). Exons 2 and 13 of *CYP3AP1* splice to the 3' end of canonical *CYP3A7* at 12 bp upstream from the translational stop codon, generating a novel *CYP3A7* variant, *CYP3A7-3AP1*. The *CYP3A7-3AP1* allele contains 15 exons encoding a longer CYP3A7 protein (CYP3A7.1L). In the putative protein, the last 4 canonical amino acids are replaced by a completely different stretch of 36 amino acids. Therefore, CYP3A7.1L is 32 amino acids longer than the product (CYP3A7.1) of canonical *CYP3A7*. As shown in Fig. 1B, intron 1-exon 2 region of 3AP1 was believed to be derived from the corresponding region of CYP3A7. However, the C flanking the heptanucleotide spacer (TTTGTAG) of *CYP3A7* intron 1 is a G in *CYP3AP1*. This nucleotide change creates an alternative splicing acceptor site of *3AP1* exon 2; thus, it converts the heptanucleotide spacer into a part of the *3AP1* exon 2, leading to a frameshift mutation of the two captured exons and thus coding a unique 36 amino acid sequence rather than the canonical CYP3A exons 2 and 13. Heterologous expression in yeast demonstrated that CYP3A7.1L has a specific activity similar to that of CYP3A7.1; whereas in the yeast expressing yeast P450 reductase, CYP3A7.1L efficiently catalyzes DHEA 7α-, 16α-, and 7β-hydroxylations, while CYP3A7.1 preferentially catalyzes DHEA 16α-hydroxylation, possibly due to the difference in the C-terminals of two enzymes [15,46].

The *CYP3A7-3AP1* transcript occurs in various adult and fetal tissues and the splicing is regulated in a developmental- and tissue-specific manner. Furthermore, *CYP3A7-3AP1* mRNA levels tend to be higher in fetal than in adult livers. In most cases, *CYP3A7-3AP1* expression is lower than that of CYP3A7, but the relative levels can vary between tissues [15,46]. The *CYP3A7-3AP1* allele is polymorphic because the splicing is abrogated by one base mutation (T > A) at position −6 upstream from the heptanucleotide spacer (TTTGTAG) (Fig. 1B). The frequency of the allele exhibits large interethnic differences: Caucasians (8%), Chinese (28%), and African Americans (59%) [53]. Although CYP3A7.1L is assumed to have a vital role in developmental, physiological and toxicological processes [53], there is little empirical evidence to support this idea. Currently, the real functions of CYP3A7.1L and its contribution to drug metabolism remain elusive.

In addition to the *CYP3A7-3AP1* allele, in fetal brain another CYP3A7 variant was also discovered, which contains sequences similar to the 3′ end of CYP3A4 intron 12 located upstream of the novel exon 13. However, no further information on this CYP3A7 variant has been reported since its initial discovery [15]. Based on the data obtained from the two variants, it is reasonable to infer that there may be additional human CYP3A7 variants awaiting discovery. The identification of potential CYP3A7 splice variants and investigation of their role in drug metabolism and fetal protection will no doubt be an intriguing topic for future research efforts.

9.3. Epigenetics

Epigenetics is an important factor in modulating the expression of many genes involved in essential liver processes [117]. By analyzing epigenetic modifications in liver tissues, He et al. illustrated that the dynamic variations of dimethylation of histone H3 at lysine 4 (H3K4me2) and H3K27me3 play a crucial role in the developmental transition of CYP3A7 to CYP3A4 [160]. Occupancy of H3K4me2 on the human *CYP3A7* promoter (−163/+103) and enhancer region (−4054/−3421 and −6265/−6247) overlapped with the glucocorticoid receptor (GR) binding site. The enriched H3K4me2 in these regions was induced by pargyline with an HNF4α or GR binding site in the *CYP3A4/3A7* gene to transactivate the corresponding genes [113].

Furthermore, cytosines in the proximal *CYP3A7* promoter were found to be hypomethylated in neonates relative to adolescents. In contrast, a −383 cytosine of *CYP3A4* was hypermethylated in liver samples from neonates compared with adolescents. The methylation status of cytosine in the *CYP3A4* and *CYP3A7* proximal promoters was observed to correlate with changes in developmental expression of mRNA for the two enzymes [161].

9.4. Cis- and trans-elements

The developmental expression of transcription factors (for instance PXR, CAR, Sp1/Sp3, USF1, NF1, HNF-3β, GR and C/EBP) as well as the interaction between these factors with the *CYP3A7* promoter may contribute to the developmental expression pattern observed with the *CYP3A7* gene [150,162-166]. The putative responsive motifs of transcription factors in the promoter region of *CYP3A7* are shown in Fig. 2.

9.4.1. Ontogeny of CYP3A7 and CYP3A4—In HepG2 cells, a nuclear factor κB (NF-κB)-like element (GGGACTTGCC) (−2326/−2297) imparted transactivation of the *CYP3A7* promoter via responsiveness to specificity proteins Sp1 and Sp3. Conversely, a *CYP3A4* NF-κB-like element (GGGACTTGAC) did not exhibit transactivation due to lacking the ability to bind Sp1/Sp3, as ascribed to a one base mutation (underlined) relative to that of *CYP3A7*. Sp1/Sp3 acted as activators of the *CYP3A7* gene via the NF-κB-like element [150]. Saffer et al. described the expression of *CYP3A7* under the control of Sp1 as regulated in a cell type- and differentiation-specific manner, with a high level in fetal livers compared with adult livers [166], implying that Sp1/Sp3 and the *CYP3A7* NF-κB-like motif may contribute to the fetal-specific expression of *CYP3A7*. It should be noted that full activation of *CYP3A7* expression also required participation of the proximal promoter. The mechanism by which Sp1/Sp3 transactivate the *CYP3A7* promoter from circa −2.3 kb remains elusive. The *CYP3A7* NFB-like element might also be recognized by other yet to be identified factors, such as complex D, which may modulate the binding activity of Sp1 for the NFB-like element [150]. Therefore, other control elements interacting with the NFB-like motif may also be essential for distal activation.

In all cell lines tested (HepG2, WRL68 and Caco-2TC7), *CYP3A4* but not *CYP3A7* exhibited responsiveness to the D-element-binding protein (DBP) [164], in combination with

the exclusive expression of DBP in adult liver [169], this may account for the occurrence of *CYP3A7* and *CYP3A4* in fetal and postnatal liver, respectively [164].

He et al. discovered that the expression level of HNF4α was most correlated with *CYP3A4* expression in the adult liver [160]; however, the expression level of GR was highly associated with *CYP3A7* expression in fetal liver. Pang et al. suggested that *CYP3A7* is developmentally regulated in mouse liver primarily by glucocorticoids through the GR [170]. In fetal hepatocytes, *CYP3A7* was found to be induced by dexamethasone but not by rifampicin, suggesting that induction was mediated by GR rather than pregnane X receptor (PXR) [103,171]. These data demonstrate that HNF4α, GR, and epigenetic changes of H3K4me2 and H3K27me3 are all associated with the ontogenic expressions of CYP3A4/3A7, and they simultaneously demonstrate that the regulation of CYP3A7 expression is very complex. Further work regarding the expression and regulation of CYP3A7 should shed some light on the mechanisms responsible for the ontological switch between CYP3A7 and CYP3A4.

As a classical example of sequential regulation of liver-enriched transcriptional factors, NF1, C/EBPα, as well as liver activator protein (LAP) and DBP, respectively, were active in early fetal, late fetal and postnatal liver, where these factors sequentially activated the human class I alcohol dehydrogenase (ADH) gene family members *ADH1, ADH2* and *ADH3* at the corresponding liver development stage. LAP and DBP maintained high-level ADH gene family transcription in postnatal liver [172]. Similar mechanisms may also control *CYP3A7* expression at various stages of hepatic growth and development.

Taking all of these data into account, we can speculate that Sp1/Sp3, GR and their respective responsive motifs may be responsible for the ontogeny of *CYP3A7*; DBP, HNF4α and their respective responsive elements may be involved in the ontogeny of *CYP3A4*; and DBP and its responsive DNA may turn on and maintain the expression of *CYP3A4* in postnatal livers. The epigenetic changes of H3K4me2 and H3K27me3 may also have some influence on the ontogeny of *CYP3A4/CYP3A7*.

9.4.2. Interindividual variation in expression of CYP3A7—The PXR and constitutive androstane receptor (CAR) are hitherto the most intensively studied transcription factors in modulating *CYP3A7*. Both were expressed at highly variable levels during early fetal life, which correlates with the highest level of *CYP3A7* expression [158,162]. PXR binds as a heterodimer with the retinoic acid receptor (RXR) to the distal xenobiotic responsive enhancer module (XREM) and proximal responsive motif (ER6), and thus activates the transcription of *CYP3A7* [149]. Similar to CYP3A4, the distal CYP3A7 XREM encompasses two conserved PXR binding sites (dNR1 and dNR2), followed by a third (dNR3), located 368 base pairs downstream of XREM. The three distal PXR binding-sites are significantly conserved between the CYP3A4 and CYP3A7 promoters with only two base pair differences [149,173]. In C3A cells, the 5′ truncated promoters (containing ER6 alone, or dNR3 plus ER6) conferred only minimal PXR-mediated induction. However, the inducibility of the promoter containing dNR1, dNR2 plus ER6 was equivalent to that of the contact promoter with all four elements (dNR1, dNR2, dNR3 and ER6), implying the importance of the XREM for PXR dependent response to xenobiotics. The dNR3 element

seemed to be negligible for xenobiotic responsiveness [149]. Interestingly, in a human colon carcinoma cell line, Burk et al. found that the CYP3A7 proximal promoter alone was all that was required to induce CYP3A7 gene expression [47]. This discrepancy may be ascribable to the difference in the cell systems examined, where each have different expression patterns of transcriptional factors. The induction functionality of CYP3A7 XREM alone has not yet been examined, whereas CYP3A4 XREM alone showed only partial activation [173]. It should be noted that the 5′-flanking regions up to approximately −8.8 kb are highly conserved between CYP3A4 and CYP3A7 [149]. We infer from this that there is cooperativity between the XREM and the ER6 of CYP3A7, which mediate the transcriptional response to xenobiotics through PXR, similarly to CYP3A4 [173].

Two kinds of ER6 elements [ER6-JMP (TTAACTcaatggAGGTCA) [174] and ER6-Itoh (TTAACTcaatggAGG-CA) [174,175] have been reported, which differ in only one base at the 3’ half site. The PXR:RXR complex can bind ER6-JMP but not ER6-Itoh [174,175], and the binding has been regarded as the mechanism underlying CYP3A7 expression [47]. This suggests a possible polymorphism of CYP3A7-ER6 responsiveness to activators.

The *CYP3A7*1C* allele is characterized by replacing 60 bp of the CYP3A7 proximal promoter with the corresponding region of the *CYP3A4* promoter. This replacement produces variation in seven bases within the proximal *CYP3A7* promoter [152], two (−165T > G; −157T > A) of which fall into ER6 motif [47], one (−127A > C) lies within the NF1/HNF3 binding site [176], and the remaining four occur in the vicinity of ER6. Therefore, the *CYP3A7*1C* promoter contains both the ER6 and NF1/HNF3 binding sites of the *CYP3A4* gene. Postnatal *CYP3A7* expression associated with the *CYP3A7*1C* allele may be ascribable to the higher affinity of binding of PXR for CYP3A4-ER6 compared with CYP3A7-ER6 [47,176]. The variation occurring in the *CYP3A7*1C* promoter results in increased activation by PXR and CAR *in vitro* and aberrant postnatal expression of *CYP3A7 in vivo*, suggesting that this region may be important for developmentally differential regulation [47]. *CYP3A7*1C* ER6 was indistinguishable, in terms of PXR regulation, from the *CYP3A7*1C* promoter with all seven mutations. The presence of *CYP3A7*1C* ER6 (CYP3A4-ER6) was necessary, and sufficient, for PXR-dependent activation of *CYP3A7*1C*. Song et al. suggested that PXR binding is dependent on the genomic context and PXR activators may modulate such binding [177].

In contrast to PXR, CYP3A4-ER6 alone is necessary, but not sufficient, for CAR-mediated activation of *CYP3A7*1C*. The full CAR-dependent activation of *CYP3A7* promoters requires the extra participation of mutated bases in the vicinity of ER6, suggesting the implication of flanking bases in the transcriptional role of CAR and additional transcriptional activators are important for *CYP3A4* or *CYP3A7* expression that interact specifically with CAR [47]. Contentious with the above findings that ER6 induced the transcription of *CYP3A7* [47,174]. Saito et al. confirmed that PXR-responsive ER6 acted as a negative regulatory motif in HepG2 cells [150]. The authors suggested that a transcriptional repressor, COUP-TF, may also bind the CYP3A7-ER6 motif, which possibly gave rise to the negative effect observed with ER6. These data suggest that additional protein-protein or protein-DNA interactions that occur through other elements may be required for full activation.

With respect to other activators, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] only weakly induced the expression of *CYP3A7*, but markedly induced *CYP3A4*. The reason for this difference was due to the fact that the binding of VDR to the proximal *CYP3A7* ER6 region was significantly less than that to the proximal CYP3A4-ER6 [178], similar to PXR and CAR.

The developmental NFI are also capable of interacting with the *CYP3A4* and *CYP3A7* proximal promoters [150,176]. However, the effect is dependent on which isoform gene is examined. NF1 can repress the transcription of *CYP3A7* via the *CYP3A7* promoter, but can also transactivate *CYP3A4* gene [150]. In addition, the expression of NF1 was found to be up-regulated postnatally [163,165]. NF1 may also play a role for the differential expression of *CYP3A7* and *CYP3A4* [176]. The YY1 element can bind to the *CYP3A4* proximal promoter and interact with NF1, but does not bind the *CYP3A7* proximal promoter [150]. Therefore, YY1 seems to be involved in the differential regulation of *CYP3A4* and *CYP3A7* through either activating or repressing transcription in a cell- and promoter-specific manner [176].

In the HepG2 cell line, HNF3 interacted with *CYP3A7* but not *CYP3A4* [150,176], which is in accordance with the fact that over-expression of HNF3 showed no effect on the *CYP3A4* proximal promoter in transfections of HepG2 or HeLa cells [168]. HNF3 was detected in all prenatal liver nuclear extracts and seemed to decrease with increasing gestational age [176]. Furthermore, it was not detected in any postnatal liver samples. This suggests that HNF3 may play a prominent part in prenatal expression of *CYP3A7*. In another study, the authors demonstrated that, in both hepatic HepG2 and non-hepatic HeLa cells, although HNF-3γ was unable to enhance the expression of *CYP3A7*, it strengthened the enhancement effect of C/EBPα in the adenoviral infected cells, which was observed to be hepato-specific. The synergism between C/EBPα and HNF-3γ in the *CYP3A4* gene has been reported to be possibly attributable to chromatin remodeling by HNF-3γ. The proximal C/EBPα site of *CYP3A7* has only one nucleotide variation relative to *CYP3A4*, and the distal C/EBPα and HNF-3γ binding sites are identical, implying that *CYP3A7* may share a similar mechanism with *CYP3A4* [168].

In HepG2 cells, USF1 was found to be the major protein bound to the E-box of *CYP3A7* or *CYP3A4*, and functioned as an activator of the *CYP3A7* proximal promoter [150]. C/EBP enhanced the binding activity of USF1 to E-box [179], and the level of C/EBP was high in mature hepatocytes relative to hepatoma cells [180]. These data may account for the differential expression of *CYP3A4* and *CYP3A7* in HepG2 cells.

When the available data is considered *en masse*, the regulation of *CYP3A7* is understood to be very complex, involving a number of transcriptional factors and responsive motifs (as summarized in Table 7). The unknown interactions among these nuclear factors and DNA elements further contribute to the regulation complexity. RNA splicing, allelic genotypes, and developmental changes in the interactions of transcription factors with the *CYP3A7* promoter may also be involved in the variable *CYP3A7* activity observed.

10. Outlook

In the ensuing decades since its original discovery, we have learned that CYP3A7 is a unique member of the CYP3A cytochrome P450 subfamily that predominates in fetal and neonatal livers, as well as some adults expressing the CYP3A7*1C allele. It is involved in the metabolism of endogenous hormones and numerous drugs and xenobiotics, exhibits great interindividual variability, and gradually decreases after birth as the developing infant liver switches to express CYP3A4. The mechanisms underlying the above-mentioned phenomena, however, remain poorly understood. In addition, some results pertaining to the developmentally differential expression of *CYP3A7* have yet to be confirmed. Despite this, there is an increasing awareness of the role epigenetics plays in the expression of CYP3A7 and how environmental factors may impact that [181]. Given the strong relationship between premature birth and environmental pollution, future studies may focus on links between CYP3A7 inhibition by pollutants and pre-term and/or low birthweight infants.

Due to the limited availability of fetal and neonatal liver samples, CYP3A7 has not been investigated in depth and has largely lagged behind the study of CYP3A4/5. Clearly, suitable replacements are sorely needed in order to study CYP3A7 and its role in growth and development as well as metabolism. In this regard, the development of new iPS hepatic stem cell line may yet prove valuable. While it has been difficult to produce hepatic iPS cell lines that accurately recapitulate adult hepatic function (primarily due to the presence of a number of fetal markers), they may more accurately represent the function of the developing neonate liver. A hepatic iPS cell line that bore the functions of the developing infant liver could prove invaluable for evaluating new or off-label use of pharmaceuticals in the neonatal population.

Regardless of the model system used, the development of a specific method for discriminating between CYP3A4/5 and CYP3A7 activities and protein content is necessary for the further study of CYP3A7 in the context of fetal liver hepatocytes or microsomes. Newer proteomics methods hold some promise in this regard. Additionally, all-trans-retinoic acid and testosterone have shown some potential application as possible non-invasive endogenous biomarkers of CYP3A7 activity.

Due to the significance of CYP3A7 in estriol biosynthesis during pregnancy and its potential to protect against exogenous toxins, a deep understanding of alleles, alternative RNA splicing, and *cis*- and *trans*-regulatory factors potentially involved in modulating CYP3A7 expression is warranted. However, there is little concrete knowledge concerning the molecular mechanisms for regulation of CYP3A7 gene expression. The current available data are inconclusive but imply a hitherto undefined complexity in the molecular regulation of CYP3A7 expression that was unexpected. However, given the clear importance of the glucocorticoid receptor, future work may focus on the possibilities of drug-drug or drug-endogenous metabolite interactions that may inhibit or induce CYP3A7 expression. This is an area of CYP3A7 research that remains underexplored and potentially may reveal some underlying mechanism of toxicity and/or developmental regulation. Additional work is also required to clarify the hierarchy of the signaling cascade regulating developmental changes and variability in the expression of nuclear factors regulating *CYP3A7*.

The modulation of *CYP3A7* expression cannot be fully elucidated unless many aspects like epigenetics, RNA splicing, developmental and differential expression of nuclear factors, the interactions between these factors and the responsive elements are taken into account. Unfortunately, until now, there has been no effective *in vitro* model for examining the regulation mechanism. Although HepG2 cells have been extensively used to investigate the mechanism of *CYP3A7* expression, HepG2 cells are subject to the limitations of the delineating roles of the transcriptional factors and response elements during development. The current available data we have obtained from *in vitro* cell models likely does not reflect conditions that actually exist in fetal livers and, hence, has only limited utility in understanding *CYP3A7* expression in the native context. A rational approach might be to initially understand the developmental expression pattern of the transcription factors in postnatal liver samples derived from different development stages, then employ various cell lines to clarify the interactions between the factors and their respective responsive elements. This strategy may facilitate elucidation of the ontogeny and differential expression of CYP3A7. In any case, given both its importance in human fetal development and drug metabolism, as well as a variety of disease states, the study of this important member of the CYP3A gene family will only increase in the future, and will likely return to us many satisfying intellectual and practical rewards.

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Abbreviations:

CYP3A7	cytochrome P450 3A7
DHEA-S	dehydroepiandrosterone sulfate
atRA	and all-trans retinoic acid
cDNA	protein produced by recombinant complementary DNA system
HFL	human fetal liver
fHLMs	human fetal liver microsomes
Hep G2	hepatocellular carcinoma cell line G2
Sp1	specificity protein 1
Sp3	specificity protein 3
HNF-3β	hepatocyte nuclear factor 3β
USF1	upstream stimulatory factor 1
XREM	xenobiotic response enhancer module

NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
HEK293 cells	human embryonic kidney cell line 293
SNP	single nucleotide polymorphism
ER6	nuclear hormone receptor binding motif 6
PXR	pregnane X receptor
CAR	constitutive androstane receptor
GR	glucocorticoid receptor
HNF-4α	hepatocyte nuclear factor 4α
NF1	nuclear factor 1
C/EBP	CCAAT-enhancer-binding protein
DBP	D-element binding protein
LAP	liver activator protein
COUP-TF	chicken ovalbumin upstream promoter-transcription factor (orphan nuclear receptor)
YY1	yin and yang 1 protein (transcription factor)

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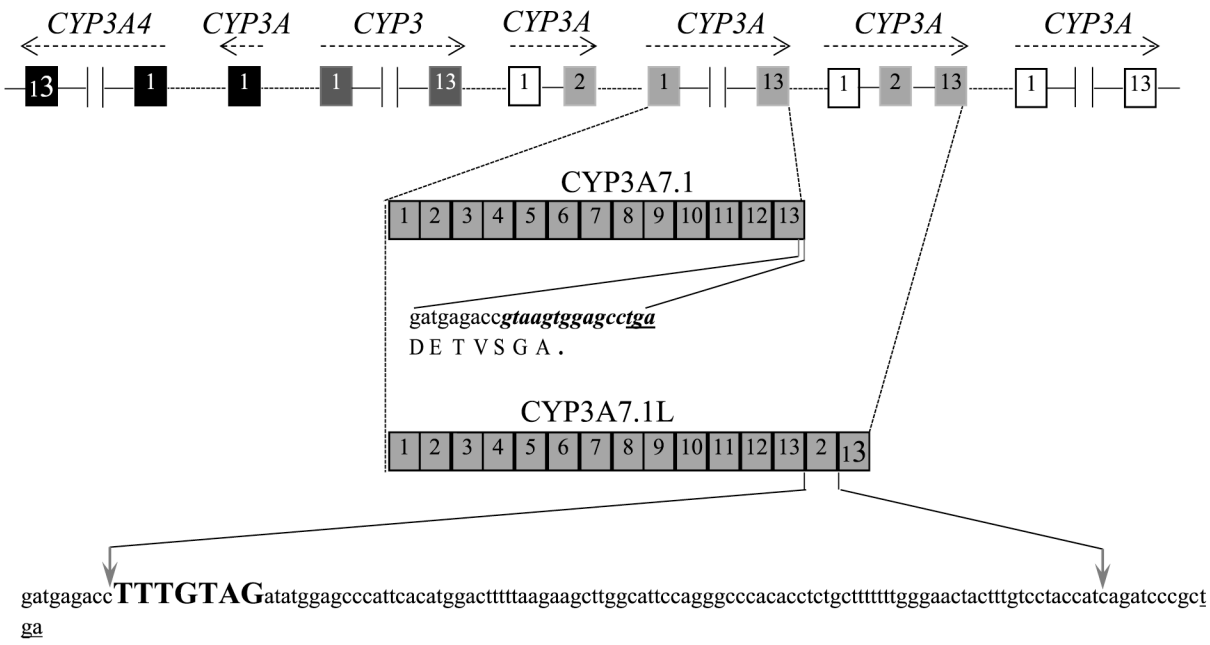
A



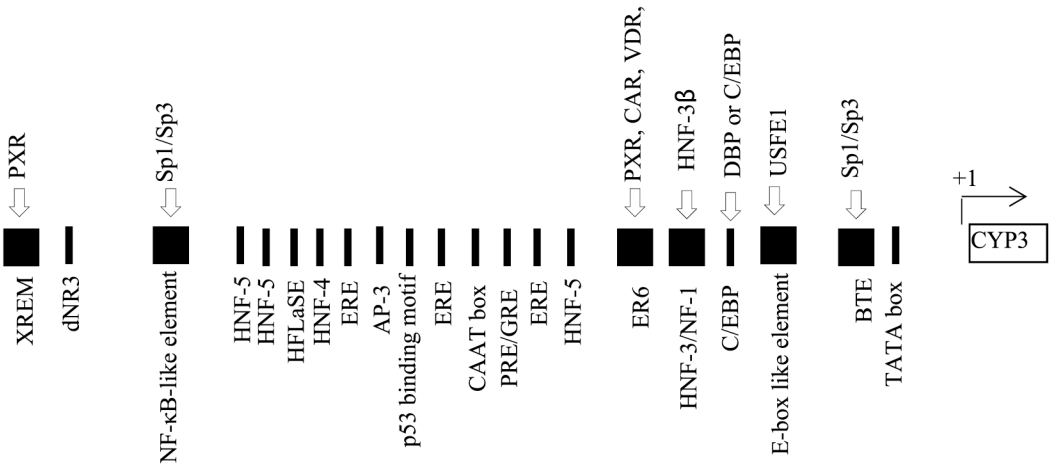
B

CYP3A7 …gacctgatttttgtttcac **tttgtag** ATATGGAACCC…
CYP3AP1_T …gacctgatttctgtttcag **TTTGTAG** ATATGGAGCCC…

CYP3AP1_A …gacctgatttctgattcag **tttgtag atatggagccc**…

Fig. 1.

Location of *CYP3A7* and its alternatively spliced variants. A: organization of *CYP3A* locus, sequences of the 3′ ends of *CYP3A7* and its variant *CYP3A7-3AP1*. The canonical *CYP3A7* last 15 bp (bold and italic) are replaced by the exons 2 and 13 of pseudogene *CYP3AP1*, generating a longer mRNA species *CYP3A7-3AP1* with extra shift-mutated sequence. B: Intron 1-exon 2 boundaries in *CYP3A7* and *CYP3AP1*. Introns and exons are shown in lowercase and in uppercase, respectively. The AG splice site of canonical *CYP3A7* exon 2 is located in the 3′-end of the heptanucleotide spacer (tttgtag)(underlined). The 5′-flanking nucleotide of the heptanucleotide spacer (bold and uppercase) is a G (boxed and shaded) in *CYP3AP1* rather than a C (boxed and shaded) in *CYP3A7*. This nucleotide variation shifts the AG acceptor splice site to an alternative site in *CYP3AP1*. The polymorphism (T > A, boxed) in *CYP3AP1* prevents the pseudogene splicing.



dNR1	TGAACTTGCTGACCC(-7707~-7693)				
dNR2	TGAAATCATGTCAGTTCA(-7663~-7646)				
dNR3	TATTATTATTGAACT(-7277~-7263)				
NF-κB-like	GGGACTTGCC(-2720~-2711)				
HNF-5	TGTTTCCA(-1011~-1004)				
HNF-5	TATTTCCA(-994~-987)				
HFLaSE	GATGGAGTG(-739~-731)				
HNF-4	AGCCAAGTCAAC(-633~-622)				
ERE	GGAAATGGTTACT(-476~-464)				
AP-3	GGGTATGAAAGG(-410~-399)				
p53 binding motif	AGGCACACTCCAGGCA(-372~-357)				
ERE	GGTAAAGATCTGT(-354~-342)				
CAAT box	GCCAAT(-259~254)				
PRE/GRE	AAGAACCCAGAACC(-232~-219)				
ERE	AGTAACATTGATT(-206~-194)				
HNF-5	TGTGTATG(-189~-182)				
ER6	TTAACTCAATGGAGGTCA(-166~-148)				
NF-1	TGATTATTTGCCAA(-132/-119)				
HNF-3	GATTATTTGC(-131/-122)				
C/EBP	ATTTGCCAAC(-127/-118)				
E-box like	CACGGG(-79~-74)				
BTE	AGCCCTGCCTCCTTCT(-49~-34)				
TATA box	TATAAA(-27~-22)				

Fig. 2.

Putative or confirmed *CYP3A7* transcriptional factors and their responsive elements. The data are collected from Refs. [45,149,150,164,167,168], respectively.

Table 1

Known substrates of the CYP3A7 enzyme.

Substrate	System	Reaction/product	Reference
Midazolam	cDNA	1- and 4-OH	[30,33]
Pentoxyresorufin	cDNA	Dealkylation	[30]
Tacrolimus	cDNA	13-O-demethylation	[61]
Retinoic Acid	cDNA/HFLM	4-OH	[62,63]
Estrone	cDNA	2-, 4-, 16α- and 6β-OH	[64]
Estradiol	cDNA	2-, 4-, 16α-, y- and 6β-OH	[33,64]
Alprazolam	cDNA	1-and 4-OH	[33]
Triazolam	cDNA	1-and 4-hydroxylation	[33]
Diltiazem	cDNA	N-Desmethyl	[33]
Clarithromycin	cDNA	N-Desmethyl, 14-OH	[33]
Nifedipine	cDNA	Oxidized	[33]
Trifluoromethylcoumarin	cDNA	7-OH	[33]
Tamoxifen	cDNA	N-Desmethyl	[33]
Sildenafil	cDNA	N-Demethylation	[65]
Tadalafil	cDNA	Demethylenation	[65]
Cisapride	fHLM/cDNA	Norcisapride, 3-fluoro-4-hydroxycisapride, 4-fluoro-2-hydroxycisapride	[66]
Luciferin 6′ benzylether	HepG2	O-debenzylation	[67]
Carbamazepine	cDNA	10,11-epoxidation	[68]
Zonisamide	cDNA	Sulfamoylacetylphenol	[68]
Glyburide	fHLMs/cDNA	Ethylene-hydroxylation	[29]
Reduced haloperidol pyridinium	Human placenta microsomes	Oxidation	[69]
Dimethyl benzoylphenylurea	cDNA	Monomethyl Dimethyl benzoylphenylurea	[70]
17α-hydroxyprogesterone caproate	cDNA/HFL	Uncharacterized metabolites M1, M2 and M3	[71]
Alfentanil	cDNA	Noralfentanil, N-phenylpropionamide	[72]
Triamcinolone acetonide	cDNA	6β-OH, Δ6-dehydrogenation	[73]
Budesonide	cDNA	6β-OH, Δ6-dehydrogenation	[73]
Fluticasone propionate	cDNA	17β-carboxy fluticasone propionate	[73]
Oleic acid	cDNA	*cis*-9,10-epoxyoctadecanoic acid	[74]

Substrate	System	Reaction/product	Reference
Carbamazepine	cDNA	Protein-reactive metabolite	[75]
3-hydroxycarbamazepine	cDNA	2,3-dihydroxycarbamazepine	[75]
Diltiazem	cDNA	N-demethylation	[76]
Cyclosporine	cDNA	ND	[77]
N-methylaniline	HFL/cDNA	N-demethylation	[11,78-80]
Ethylmorphine		N-demethylation	
N,N-dimethylnitrosamine		N-demethylation	
Benzphetamine		N-demethylation	
Meperidine		N-demethylation	
Aminopyrine		N-demethylation	
N,N-dimethylaniline		N-demethylation N-oxidation	
Chlorpromazine		N-demethylation Hydroxylation N-oxidation	
Diazepam		N-demethylation Hydroxylation	
Medazepam		N-demethylation Hydroxylation	
Prazepam		N-demethylation Hydroxylation	
Aniline		Hydroxylation	
Desmethylimipramine		Hydroxylation	
Hexobarbital		Hydroxylation	
Caffeine		Hydroxylation	
Diphenylhydantoin		Hydroxylation	
Biphenyl		4-hydroxylation 2-hydroxylation	
2,5-diphenyloxazole		Hydroxylation	
2-acetylaminofluorene		Hydroxylation N-hydroxylation	
Benzo(*a*)pyrene		Hydroxylation Epoxidation Quinone formation	
Aldrin		Epoxidation	
Carbamazepine		Epoxidation	

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Substrate	System	Reaction/product	Reference
p-nitrobenzoic acid		Nitro reduction	
p-nitroanisole		O-deethylation	
7-ethoxycoumarin		O-deethylation, N-demethylation	
6-aminochrysene		Metabolic activation	
Aflatoxin B1		Metabolic activation	
Sterigmatocystin		Metabolic activation	
2-amino-3-methylimidazo-(4,5-f)quinoline		Metabolic activation	
2-amino-6-methyldipyrido-(1,2-a:3′2′-d)imidazole		Metabolic activation	
Progesterone	HLM/cDNA	6β-OH, 16α-OH	[81]
Bile acid	cDNA	1β–OH–deoxycholic acid	[82]
Sildenafil	cDNA	N-demethylation	[65]
Tadalafil	cDNA	Demethylenation	[65]

*cDNA, protein produced by recombinant complementary DNA system; HFL, human fetal liver; fHLMs, human fetal liver microsomes; Hep G2, hepatocellular carcinoma cell line G2; HFL, human fetal liver; ND, not determined.

Table 2

(Potential) biomarker compounds of CYP3A7.

Probe	Marker reaction	Reference
DHEA-S	16α-hydroxylation	[28,84]
Testosterone	6β-hydroxylation, 2α-hydroxylation	[34,54,60]
All-trans-retinoic acid	4-OH, 18-OH or 4-oxo	[62,83]

Table 3

Inhibitors of human CYP3A7 activity.

Inhibitor	Substrate reaction	Reference
Triacetyloleandomycin	N-demethylation	[19]
α-naphthoflavone	Imipramine N-demethylation	[19]
Troleandomycin	*all-trans*-retinoic acid 4-hydroxylation	[62]
Estradiol	Carbamazepine 10,11-epoxidation	[32]
Triazolam	Testosterone 6β-hydroxylation	[68]
Amprenavir	Testosterone 6β-hydroxylation	[36]
Indinavir	Testosterone 6β-hydroxylation	[36]
Nelfinavir	Testosterone 6β-hydroxylation	[36]
Ritonavir	Testosterone 6β-hydroxylation	[36]
Saquinavir	Testosterone 6β-hydroxylation	[36]
Azamulin	7-benzyloxy-4-trifluoromethylcoumarin	[88]
Ketoconazole	7-benzyloxy-4-trifluoromethylcoumarin	[87,88]
Δ^9-tetrahydrocannabinol	Diltiazem N-demethylation	[76]
Cannabidiol	Diltiazem N-demethylation	[76]
Cannabinol	Diltiazem N-demethylation	[76]
Olivetol	Diltiazem N-demethylation	[76]
Hop-Containing products	Dibenzylfluorescein, 7-ethoxy-3-cyanocoumarin, 7-methoxy-4-trifluoromethylcoumarin	[89]
West African medicinal and food plants	Dibenzylfluorescein	[90]
Melatonin products	NA	[91]
Astemizole Cisapride Clotrimazole Cyclosporine A Erythromycin Ketoconazole Mibefradil Midazolam Nicardipine Nifedipine Nimodipine Terfenadine Troleandomycin Verapamil	7-benzyloxy-4-trifluoromethylcoumarin O-dealkylation	[92]

*NA, not available.

Table 4

Activators of human CYP3A7.

Activator	Test system	Substrate reaction	Reference
Androstenedione	cDNA	Carbamazepine	[32]
DHEA-S	cDNA	10,11-epoxidation	
Pregnenolone-S	cDNA		
17α-hydroxypregnenolone-S	cDNA		
α-naphthoflavone Testosterone	cDNA	7-benzyloxy-4-trifluoromethylcoumarin-O-dealkylation	[92]

Table 5

Inducers and suppressors of the expression of CYP3A7.

Chemical	Host	Up/Down regulation of expression	Reference
Dexamethasone	HepG2/fetal hepatocytes	Up	[101,103]
Betamethasone	Fetal hepatocytes	Up	[103]
Prednisolone	Fetal hepatocytes/HepG2	Up	[103,104]
Methylprednisolone	Fetal hepatocytes	Up	[103]
Fludrocortisone	Fetal hepatocytes	Up	[103]
Rifampicin	HepG2	Up	[104]
Phenytoin	HepG2	Up	[104]
Clotrimazole	HepG2	Up	[104]
Cyclosporine	HepG2	Up	[104]
Carbamazepine	HepG2	Up	[104]
Phenobarbital	HepG2	Up	[104]
4-monochloropheno	HepG2	Up	[105]
Beclomethasone dipropionate	DPX2	Up	[106]
Endosulfan	HepG2	Up	[107]
Chemotherapeutic agents (cisplatin, etoposide or doxorubicin)	HepG2	Up	[108]
Pentachlorophenol	HepG2	Up	[109]
U0126	HepG2	Up	[110]
Maternal smoking	Fetal livers	Up	[111]
Apple polyphenols extract	Colon adenoma LT97 cell	Up	[102]
Neonicotinoids (thiacloprid, thiamethoxam, imidacloprid)	H295R cells	Up	[112]
Pargyline	Human primary fetal liver cells, HepG2	Up	[113]
Chronic cadmium exposure	HepG2	Up	[114]
Rifampicin	HepG2, hepatocytes	Up	[115,116]
Troleandomycin	HepG2	Up	[116]
Erythromycin	HepG2	Up	[116]
Phenobarbital	HepG2	Up	[116]
Phenobarbital-like inducers	HepG2	Up	[116]
Lovastatin	HepG2	Up	[116]

Chemical	Host	Up/Down regulation of expression	Reference
5-aza-2′-deoxycytidine	HepG2	Up	[117]
St. John's wort	HepG2	Down	[101]
Troglitazone	HepG2	Down	[118]
Acute cadmium exposure	HepG2	Down	[114]

Up: upregulated; down: downregulated.

Table 6

Alleles of CYP3A7.

Allele	Protein	SNP[a]	Position	Effect	Ethnic and frequency %	Reference
*CYP3A7*1A*	CYP3A7.1, CYP3A7.1L	None				[12,46]
*CYP3A7*1B*	CYP3A7.1	−211 C > T	Promoter	Increased expression	Brazilian, 0.4 Caucasians, 1.0 African Americans, 0	[151] [47,152] [152]
*CYP3A7*1C*	CYP3A7.1	−186G > T; −179T > A; −177T > C; −176A > T; −165T > G; −157T > A; −127 A > C	Promoter	Increased expression	Brazilian, 1.2–3.3 Caucasians, 2.7–3.9 African Americans, 6.0 Korean, 0 Jordanian, 1.7 Samples Brussels, 4 Liver samples from UK, 6	[136,151] [47,77,139,143,144,152] [152] [153] [154] [155] [156]
*CYP3A7*1D*	CYP3A7.1	+13 G > A	+13		Brazilian, 0.4 Caucasian, 1 African Americans, 0	[151] [47,152] [152]
*CYP3A7*1E*	CYP3A7.1	+55 G > A	+55		Brazilian,2.2 Fetal livers, 3.7 African Americans, 8 Caucasians, 0 Caucasian-Americans, 2.6	[151] [60] [153] [152,153] [60]
*CYP3A7*2*	CYP3A7.2	26041C > G	Exon 11	T409R	Koreans, 26.0 Caucasians, 8.0–10.5 Tanzanians, 62.0 Chinese, 28 Saudi Arabian, 17 Brazilian, 25 Fetal livers, 37.8	[153] [53,157] [53] [53] [53] [151] [60]
*CYP3A7*3*	CYP3A7.3	4011insT	Exon 2	Frameshift	Korean, 0.21	[153]

[a]The numbers are relative to the transcription start site in the CYP3A7 gene, which is defined as +1.

Table 7

Genetic regulatory mechanisms: CYP3A4 vs. CYP3A7.

Nuclear Receptor/Transcription Factor NRNC Abbreviation:	Nuclear Receptor/Transcription Factor Full Name:	CYP3A4	CYP3A7
PXR	Pregnane X receptor	Yes	Yes
CAR	Constitutive Androstane receptor	Yes	No
FXR	Farnesoid X receptor	Yes	No
Sp1	Specificity protein 1	?	Yes
Sp3	Specificity protein 3	?	Yes
USF1	Upstream stimulatory factor 1	?	Yes
NF1	Nuclear factor 1	Yes	Yes
HNF-3β	Hepatocyte nuclear factor 3β	Yes	Yes
HNF-4α	Hepatocyte nuclear factor 4α	Yes	Yes
GR	Glucocorticoid receptor	No	Yes
C/EBP	CCAAT enhancer binding protein	Yes	Yes
NFkB	Nuclear factor kappa light chain enhancer of activated B cells	Yes	Yes
XREM	Xenobiotic response enhancer module	Yes	Yes
DBP	D-element binding protein	Yes	No