

# Transcription Factors Potentially Involved in Regulation of Cytochrome P450 Gene Expression

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## 1. Introduction

Drug-metabolizing enzymes, including the cytochrome P450 (CYP) superfamily of enzymes, are subject to regulation by both exo- and endogenous factors, mostly hormones and cytokines (Monostory et al., 2009; Waxman & Chang, 2005). In this regulation transcription factors are the mediators. Among them, orphan nuclear receptors: CAR (*Constitutive Androstane Receptor*), PXR (*Pregnane X Receptor*), VDR (*Vitamin D Receptor*), FXR (*Farnesoid X Receptor*), LXR (*Liver X Receptor*), PPAR $\alpha$  (*Peroxisome Proliferator-Activated Receptor  $\alpha$* ) and RXR (*Retinoid X Receptor*) are the most important. They can create heterodimers in any configuration what, in conjunction with a broad spectrum of attached ligands, reflects the complexity of regulatory networks (Honkakoski & Negishi, 2000; Xu et al., 2005). Expression of some CYP isoforms is dependent on gender, which partly explains the metabolic difference between men and women in pharmacokinetics of drugs or, for instance, in susceptibility to carcinogens (Scandlyn et al., 2008). The main role in the sex-dependent regulation of CYP expression plays the growth hormone (GH) and to a lesser extent - other hormones. In principle, there are significant differences between genders in the daily profile of GH secretion into the bloodstream (Waxman & Chang, 2005). GH activates signaling pathway JAK-STAT (Lobie & Waxman, 2003). The main regulator of hepatic gene expression dependent on GH is transcription factor STAT5b which, together with other co-regulators (i.e. HNF-4 $\alpha$ ) can stimulate CYP genes directly by the binding to promoter sequences of target genes or indirectly by the activation of gene expressions of the gender-specific transcription factors (Park et al., 2006). As a result, in transactivation of cytochrome P450 genes, we can distinguish at least two pathways: (1) metabolic, dependent on the type of xeno- or endobiotic, mediated by several nuclear receptors and (2) signaling, associated with activation of numerous GH-dependent transcription factors. Therefore, some endocrine disorders may cause changes in the drug metabolism, as well as in the CYP-dependent metabolism of endogenous substrates.

## 2. Regulation of cytochrome P450 gene expression by the nuclear receptors

Cytoplasmic and nuclear receptors participate in the regulation of cytochrome P450 genes expression (table 1). Best known is the aryl hydrocarbon receptor (AhR), which being

inactive in the cytosol remains associated with several co-chaperones: Hsp90 (*Heat shock protein-90*), XAP2 (*Hepatitis B virus X-associated Protein 2*) and the co-chaperone p23, regulating ligand-dependent nuclear import and protecting AhR from ubiquitination and further proteolysis (Monostory et al., 2009). Upon ligand binding to AhR, the cytosolic complex with chaperones dissociate, allowing the receptor phosphorylation by stimulated tyrosine kinase and translocation of AhR/ligand complex to the nucleus. In the nucleus, binding with ARNT (*AhR Nuclear Translocator*) protein into the heterodimer and interaction of the activated AhR/ARNT complex with the respective XRE (*Xenobiotic Response Element*) sequences located in the CYP genes, takes place (Honkakoski & Negishi, 2000; Monostory et al., 2009).

Nuclear receptors: CAR, PXR, RXR, VDR, FXR, LXR and PPAR $\alpha$  participate in the complex regulation of CYP gene transcription, as transcription factors activated by ligand. Frequently they are activated in the cytoplasm and then translocated to the nucleus, where they form a heterodimer with RXR. These receptors are third class of nuclear hormone receptors, called xenoreceptors (XR) or xenosensors (Xu et al., 2005).

CAR binds to RXR into the heterodimer, which after binding to coactivators, interacts with the relevant regulatory sequences of target genes, mostly with the module sensitive to retinoic acid - RARE (*Retinoic Acid Response Element*). In the case of phenobarbital induction the formed heterodimer binds to the NR1 sequence (*Nuclear Receptor binding site 1*) being a part of PBRU (*Phenobarbital-Responsive enhancer Unit*) - multicomponent enhancer necessary to run the phenobarbital-dependent gene expression. In turn, the binding of CAR with natural ligand causes a loss of its activity (Czekaj, 2000).

PXR participates in the response to the numerous and structurally diverse xenobiotics. Dimeric complex PXR/RXR interacts with AGTTCA sequence in CYP3A1/2 genes separated by a trinucleotide spacer (DR3, *Direct Repeat-3*), and with XREM (*Xenobiotic-Response Enhancer Module*) and ER6 (*Everted Repeat with a 6-nucleotide spacer*) in the CYP3A4 gene. PXR gene polymorphism is probably one of the reasons for varied response to pharmacotherapy and the incidence of side effects in the population (Lamba & Schuetz, 2009).

VDR heterodimerizes with RXR and the formed complex can bind sequences of human CYP3A4 gene: pER6 (*proximal Everted Repeat with a 6-nucleotide spacer*) and dXREM (*distal Xenobiotic-Responsive Enhancer Module*), increasing its expression (K. Wang et al., 2008). Through the influence on CYP3A4 - the main enzyme metabolizing drugs in the intestine - VDR is a potential modulator of first-pass effect in the gastrointestinal tract. Moreover, it can be stimulated by bile acids and interact with FXR, as calcitriol inhibits transactivation of genes regulated by this receptor. VDR can form complexes with p65 subunit of NF $\kappa$ B factor (*Nuclear Factor kappa-light-chain-enhancer of activated B cells*) and thereby inhibit gene expression of proinflammatory proteins (Levi, 2011).

FXR regulates the expression of genes as a FXR/FXR homodimer or FXR/RXR heterodimer. FXR, through the CYP3A11 gene induction, CYP7A1 gene repression, and induction of expression of ileal bile acid binding protein (IBABP), inhibits the biosynthesis of bile acids and increases their transport from the intestine to the liver. High content of FXR in tissues associated with enterohepatic circulation makes it a regulator of drug distribution in the body (Gnerre et al., 2004; X. Wang et al., 2009).

Receptor		Natural ligands	Synthetic ligands	Response elements in CYP gene promoters (target sequence, spacer orientation and length)	Cytochrome P450 genes regulated by receptor	Receptor-dependent function	References
Abbreviation (NRNC symbol)	Full name (year of description)						
AhR	Aryl hydrocarbon Receptor (1992)	Tryptophan derivatives, bilirubin, metabolites of arachidonic acid, e.g.: prostaglandin G and lipoxin A4, carotenoids	Polycyclic and halogenated aromatic hydrocarbons	AHRE, DRE, XRE ( <i>GCGTG</i> )	Human: <i>CYP1A1, CYP1A2, CYP1B1</i> Rat: <i>CYP1A1, CYP1A2, CYP1B1</i>	Xenobiotic metabolism, cell proliferation and differentiation	(Cui et al., 2009; Honkakoski & Negishi, 2000)
CAR (NR1I3)	Constitutive Androstane Receptor (1994)	Metabolites of 3 $\alpha$ ,5 $\alpha$ -androstane; androstano and androsteno (reverse agonists), DHEA	Phenobarbital, CITCO, TCPOBOP	CARE, RARE, PBRU ( <i>AGGTC</i> ); DR3, DR4, DR5, ER6, ER8)	Human: <i>CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP4A</i> Rat: <i>CYP2B1, CYP2B2</i>	Xenobiotic metabolism, regulation of lipid and energy metabolism, bile acid metabolism, heme synthesis, cholestasis, tumor promotion, hepatotoxicity	(Chen et al. 2010; Phillips et al., 2007; Xu et al., 2005)
PXR/SXR (NR1I2)	Pregnane X Receptor (rodent)/Steroid and Xenobiotic Receptor (human) (1998)	21-carbon steroids, so-called pregnans, e.g.: pregnenolone; progesterone, corticosteroids, estrogens, DHEA	Numerous xenobiotics, e.g.: phenobarbital, rifampicin, dexamethasone	XREM ( <i>AGTTC</i> ); DR3, DR4, ER6, ER8, IR0)	Human: <i>CYP1A, CYP1B, CYP2A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP3A7, CYP4F</i> Rat: <i>CYP3A1, CYP3A2, CYP3A9, CYP3A18, CYP3A23</i>	Xenobiotic metabolism, regulation of lipid and bile acid metabolism, cholestasis, heme synthesis	(Honkakoski & Negishi, 2000; Takagi et al., 2008; Xu et al., 2005)
VDR (NR1I1)	Vitamin D Receptor (1988)	1,25 dihydroxyvitamin D <sub>3</sub> - 1,25(OH) <sub>2</sub> D <sub>3</sub> , lithocholic acid, curcumin, polyunsaturated fatty acids,	Doxercalciferol, paricalcitol	VDRE, $\alpha$ XREM ( <i>PtGGTTC</i> ); DR3, DR4, DR5, DR6, pER6)	Human: <i>CYP2B6, CYP2C9, CYP3A4, CYP24, CYP27B1</i> Rat: <i>CYP24A1, CYP27A1, CYP27B1</i>	Calcium homeostasis, cell proliferation and differentiation, immunological response	(Honkakoski & Negishi, 2000; Levi, 2011; K. Wang et al., 2008; Zhang et al., 2010)

Table 1. Important receptors regulating cytochrome P450 expressions.

Receptor		Natural ligands	Synthetic ligands	Response elements in CYP gene promoters (target sequence, spacer <sup>1</sup> orientation and length)	Cytochrome P450 genes regulated by receptors	Receptor-dependent function	References
Abbreviation (NRNC symbol)	Full name (year of description)						
FXR (NR1H4)	Farnesoid X Receptor/Bile Acids Receptor (1995)	Bile acids, e.g.: chenodeoxycholic acid	Farnesol, GW4064, INT-747	FXRE (AGTTCAnTGAATCT; DR4, ER8, IR1, IR0)	Human: CYP3A4, CYP7A1, CYP8B1 Rat: CYP7A1	Bile acid metabolism, regulation of lipid and carbohydrate metabolism	(Gierre et al., 2004; Kemper et al., 2009; Thomas et al., 2008)
LXR $\alpha$ (NR1H3)	Liver X Receptor- $\alpha$ (1995)	Endogenous oxysterols: 22(R) and 24(S)-hydroxycholesterole, 24(S)-epoxycholesterole and 7 $\alpha$ -hydroxycholesterole	GW3965, DMHCA	LXRE (AGTTC $\alpha$ ; DR4)	Human: CYP7A1 Rat: CYP7A1, CYP46A1, CYP51A1	Cholesterol and bile acid metabolism	(Honkakoski & Negrishi, 2000; Levi, 2011; Thomas et al., 2008; Wagner et al., 2011)
PPAR $\alpha$ (NR1C1)	Peroxisome Proliferator-Activated Receptor- $\alpha$ (1990)	Polyunsaturated fatty acids and PFA derivatives: prostaglandins, eicosanoids and leukotrienes, DHEA	Fibrates, e.g.: fenofibrate, bezafibrate, clofibrate	PPRE (AGGTCA; DR1, DR2)	Human: CYP1A, CYP2A, CYP2C, CYP2E, CYP4A, CYP7A1, CYP8B1, CYP27 Rat: CYP4A1	Cholesterol and bile acid metabolism, regulation of carbohydrate metabolism and inflammation	(Li & Chiang, 2009; Paumelle & Staelens, 2007; Rigamonti et al., 2008; Zheng et al., 2010)
RAR $\alpha$ (NR1B1)	Retinoic Acid Receptor- $\alpha$ (1987)	Vitamin A derivatives: all-trans (atRA) and 9-cis (9cRA) retinoic acid isomers, and other retinoids	Am 580, CD367	RARE (P $\alpha$ GTG/TTC $\alpha$ ; IP-8, DR1, DR2, DR5)	Human: CYP26A1 Rat: CYP1A, CYP2C7, CYP26	Cell proliferation and differentiation, morphogenesis	(Alvarez et al., 2011; Honkakoski & Negrishi, 2000)
RXR $\alpha$ (NR2B1)	Retinoid X Receptor- $\alpha$ (1990)	Vitamin A derivative: 9-cis (9cRA) retinoic acid isomer and other retinoids, eicosanoids, phytanic acid	Methoprene, LGD1069, LG100268	RXRE (AGGTCA; DR1, DR2, DR3, DR4, DR5, IR0)	Genes dependent on nuclear receptors heterodimerizing with RXR	Cell proliferation, processes dependent on nuclear receptors heterodimerizing with RXR	(Chen et al., 2010; Perez et al., 2011; K. Wang et al., 2008; Xu et al., 2005)

Table 1. Important receptors regulating cytochrome P450 expressions (Continuation).

LXR, after joining the ligand, heterodimerization with RXR and binding of the complex with the promoter of CYP7 gene coding element of steroid 7 $\alpha$ -hydroxylase, acts as a 'sensor' of cholesterol concentration, by stimulating its removal from the liver. Lack of LXR inhibits conversion of cholesterol into bile acids (Thomas et al., 2008; Wagner et al., 2011).

PPAR $\alpha$  is most commonly associated with the mechanism of CYP4 gene family expression (Li & Chiang, 2009). After binding to ligand and heterodimerization with RXR, FXR, or LXR joins a PPRE (*Peroxisome Proliferator Response Element*) sequence, located in the promoter of target genes. PPAR $\alpha$  is currently the subject of numerous pharmacological and pharmaceutical studies, as it is the target or it modulates the activity of many groups of commonly used hypolipemic and antidiabetic drugs: fibrates, glitazones and statins (Paumelle & Staels, 2007).

RXR, through the creation of numerous heterodimers, has a co-regulatory function as a nuclear auxiliary protein (NAP). There are two types of RXR heterodimers: a 'permissive', such as PPAR/RXR, LXR/RXR, FXR/RXR, activated freely by RXR ligands or his partner's ligands; and the 'nonpermissive' type, such as RAR/RXR, VDR/RXR and T $_3$ R/RXR dimers, where only the ligands of bound orphan proteins are the activator (Xu et al., 2005). The fact that the receptors CAR, PXR, VDR, FXR, LXR and PPAR form heterodimers in any configuration with the same RXR protein related to the metabolism of endobiotics, makes him a 'connector' of various metabolic pathways in the body (the phenomenon of interference - 'cross-talk') and gives a picture of a complex regulatory network.

Currently, intensively investigated are epigenetic modifications of cytoplasmic and nuclear receptors, which include DNA methylation, modifications of histones and regulation by microRNA (Klaassen et al., 2011). AhR is under the epigenetic regulation consisting of hypermethylation of promoter region of AhR gene (Cui et al., 2009). Such regulation occurs in acute lymphoblastic leukemia and impairs binding of the transcription factor Sp1 to the AhR promoter and, as a result, the initiation of transcription (Mulero-Navarro et al., 2006). In mouse models of obesity and diabetes type II increased acetylation of FXR protein can be observed (Kemper et al., 2009). MicroRNA (miRNA) may regulate signaling pathways of nuclear receptors on three levels, through direct interaction with 3'UTR mRNA sequence of: nuclear receptor, and/or co-regulators, or target genes (Pandey & Picard, 2009). It has been proven that the miR-148a causes post-transcriptional down regulation of PXR, which results in a lower induction of CYP3A4. Therefore, the levels of PXR mRNA and protein did not correlate with each other in normal human liver (Takagi et al., 2008). In the studies on the CAR receptor it has been shown that in precancerous, phenobarbital-induced lesions in the wild-type mice, disorders of gene methylation are present, in contrast to mice with silenced gene CAR (Philips et al., 2007). More and more evidences indicate the regulation of PPAR $\alpha$  by miR-10b, depending on binding site in the 3'UTR sequence. miR-10b may be a new player in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and a new target for drugs in the treatment of this disease (Zheng et al., 2010). It has also been shown that expression of VDR, stimulated by ligand attachment - 1,25(OH) $_2$ D $_3$ , is inhibited by miR-125b, miR-27b and mmu-miR-298 (Mohri et al., 2009; Pan et al., 2009).

### 3. Regulation of cytochrome P450 gene expression dependent on the growth hormone

#### 3.1 Growth hormone and the transduction of its signal

The main role in the sex-dependent regulation of CYP expression plays the growth hormone (GH) and to a lesser extent – other hormones. Growth hormone, also called somatotrophic hormone (STH), is a 21.5 kDa protein secreted into the blood by acidic somatotrophs of the anterior pituitary. The release of this hormone is regulated by hypothalamic peptides, which means it is stimulated by somatotropin – GHRH (*Growth Hormone-Releasing Hormone*) and inhibited by somatostatin – GHIH (*Growth Hormone-Inhibiting Hormone*; SST). It is also regulated by other hormones and neurotransmitters, such as ghrelin (the strongest stimulator), leptin, sex hormones, corticosteroids, or dopamine (Veldhuis et al., 2006; Wójcikowski & Daniel, 2011). GH shows strong anabolic properties by stimulating the biosynthesis of proteins and nucleic acids, and insulin secretion, but also shows catabolic properties by stimulating lipolysis (Veldhuis et al., 2006).

In male rats the secretion of GH is a pulse type. Every 3.5–4 h the hormone concentration in blood reaches value up to 200 ng/ml, however outside these periods it is very low or even undetectable. To invoke the proper cellular response the impulse frequency, duration and amplitude are important. In females there is no clear pulsation and the average hormone concentration in serum is 30-60 ng/ml (Waxman & Chang, 2005).

The growth hormone receptor (GHR) is the integral cell membrane protein, by which GH has a direct impact on the cells of the liver, skeletal muscles, bones, brain, and adipose tissue (Rosenfeld & Hwa, 2009). On the surface of female hepatocytes there are much more GHRs, which probably play a role in different response to GH comparing to males (Waxman & Chang, 2005). Binding GH to the receptor causes its dimerization, and activation of JAK2 (*Janus-type Tyrosine Kinase-2*) tyrosine kinase initiating several signaling pathways. The main mechanism of GH-dependent transcriptional regulation is based on the JAK-STAT, pathway in which STAT (*Signal Transducers and Activators of Transcription*) proteins 1, 3, 5a and 5b are involved (Lobie & Waxman, 2003; Rosenfeld & Hwa, 2009). In addition, the small Ras (*Rat sarcoma viral oncogene*) proteins, the family of MAPK (*Mitogen-Activated Protein Kinases*), IRS-1-3 (*Insulin Receptor Substrates*) adapter proteins, GRB-2 (*Growth factor Receptor-bound protein 2*), SHC (*Src Homology/Collagen homology*); SOS (*Son of Sevenless*) protein, the protein kinase C (PKC) and phosphatidylinositol-3 kinase (PI 3-kinase) are activated. GH may also activate the epidermal growth factor receptor (EGFR) and non-receptor kinases: c-Src, c-Fyn and FAK (Lobie & Waxman, 2003). Indirectly, GH affects tissues through insulin-like growth factors: IGF-I and IGF-II, (GH/IGF axis), which are produced primarily in the liver (Veldhuis et al., 2006). In the external regulation of growth signal, CIS (*Cytokine-inducible SH2 protein*) and SOCS (*Suppressors of Cytokine Signaling*) proteins, are involved. They are regulated by proinflammatory interleukin 6 (IL-6) and concentration of these proteins increases in various pathological conditions, such as rheumatic diseases (MacRae et al., 2006).

#### 3.2 Regulation of transcription factors gene expression dependent on the growth hormone

In 2008, sex-dependent genes expressed in the liver of hypophysectomized rats administered GH were examined by means of the DNA microarrays technique (Wauthier &

Waxman, 2008). Twenty four of 1032 genes were identified as early response genes, candidates for direct targets of GH action. 15 of them underwent induction and 9 - inhibition under the influence of GH (table 2). There were no cytochrome P450 genes among them, however, there were genes of transcription factors participating in their regulation, e.g. Bcl6, Cutl2, HNF-6 and PPAR $\gamma$  (described below), as well as Egr1, Myc and Nr0b2/SHP. It was also confirmed that GH maintains the hepatic sexual dimorphism, by means of both positive and negative regulatory mechanisms. In mouse liver, 88% of male-specific genes were subject to positive regulation by pituitary hormones, whereas in females, most genes (64%) were under negative regulation (Wauthier et al., 2010).

Gene symbol (alphabetical order)	Gene name	Response to GH	Sex-specific gene class	Involvement in CYP regulation
Asb9	Ankyrin repeat and SOCS box-containing protein 9	Suppression	none	no data
Bcl3	B-cell leukemia/lymphoma 3	Induction	none	no data
Bcl6	B-cell leukemia/lymphoma 6	Suppression	Male class IIA	yes
Cux2	Cutl2, Cut-like 2	Induction	Female class IA	yes
Egr1	Early growth response 1	Induction	none	yes
Etv6	Ets variant gene 6 (TEL oncogene)	Induction	none	no data
Foxq1	Forkhead box Q1; HFH-1	Induction	none	no data
Hhex	Hematopoietically expressed homeobox	Induction	none	no data
Jun	Jun oncogene	Induction	none	no data
Klf9	Kruppel-like factor 9	Induction	none	no data
Klf15	Kruppel-like factor 15	Suppression	none	no data
Lef1	Lymphoid enhancer binding factor 1	Suppression	none	no data
Lhx1	LIM homeobox protein 1	Suppression	none	no data

Gene symbol (alphabetical order)	Gene name	Response to GH	Sex-specific gene class	Involvement in CYP regulation
Msx1	Homeo box, msh-like 1	Induction	none	no data
Myc	Myelocytomatosis viral oncogene homolog (avian)	Induction	none	yes
Ncl	Nucleolin	Induction	Female class IB	no data
Nfyb	Nuclear transcription factor-Y beta	Induction	none	no data
Nr0b2	Nuclear receptor subfamily 0, group B, member 2; SHP	Suppression	none	yes
Onecut1	One cut domain, HNF6	Induction	Female class IB	yes
Pou3f3	POU domain, class 3, transcription factor 3	Induction	none	no data
Pparg	Peroxisome proliferator activated receptor gamma	Suppression	Male class IIB	yes
Tbx3	T-box 3	Suppression	none	no data
Zfp37	Zinc finger protein 37	Induction	Male class IA	no data
Zfp786	Zinc finger protein 786	Suppression	none	no data

Table 2. Early GH response genes of the DNA-binding proteins and transcription factors.

Well recognized examples of sex-specific transcription factors are: Tox (*Thymus high-mobility group box protein*), Cutl2 (*Cut-like 2*), and Trim 24 (*Tripartite motif-containing 24*). They undergo preferential expression in the liver of female rats, where their levels are accordingly 16, 125 and 73 times higher than those found in males. Both, Tox and Cutl2 belong to the GH response genes. Tox is a protein involved in the regulation of T lymphocytes maturation. Cutl2 (Cux2) is one of the early GH response genes and plays a role in the control of proliferation and differentiation of nervous tissue cells (Wauthier & Waxman, 2008). Trim 24 (TIF1 $\alpha$ ) participates in chromatin remodelling and thus controls its transcriptional activity. The expression of all three genes is increased, at least to the 'female' levels, in secondary feminized males (Laz et al., 2007).

Bcl6 (*B-cell leukemia/lymphoma 6 protein*) is a specific to males transcriptional repressor, whose binding with DNA increases significantly between GH pulsations, when the binding



of the STAT5 factor is low. On the basis of studies on Bcl6, a new mechanism of GH-dependent sex specificity has been described (Meyer et al., 2009). The analysis of primary transcripts (hnRNA) showed that in females, in contrary to males, there comes to the dual block during the process of Bcl6 elongation: in the intron 4 and exon 5.

### 3.3 Regulation of cytochrome P450 gene expression by growth hormone

Sex-specific genes in rat liver were divided into two classes, depending on the character of the response to GH secretion pattern: class I genes, down-regulated in one, or both sexes after hypophysectomy and thus required pituitary hormones for full expression and class II genes, up-regulated in one or both sexes after hypophysectomy and thus suppressed by pituitary hormones (Wauthier & Waxman, 2008; Waxman & Chang, 2005; Waxman & Holloway, 2009). Additionally, these classes of genes were divided into subclasses. Male-specific genes into: class IA - down-regulated in males, but not in females; class IB - down-regulated in both males and females; class IC - down-regulated in males, but up-regulated in females; class IIA - selectively up-regulated in females; class IIB - up-regulated in both males and females. Female-specific genes into: class IA - down-regulated in females, but not in males; class IB - down-regulated in both males and females; class IC - down-regulated in females, but up-regulated in males; class IIA - selectively up-regulated in males; class IIB - up-regulated in both males and females (Wauthier & Waxman, 2008).

Class I, obligatorily dependent on GH pulsation includes 'male' CYP2C11 isoform (testosterone 2 $\alpha$ - and 16 $\alpha$ -hydroxylase). CYP2C11 expression does not occur in young animals and is induced only during sexual maturation. A similar dependence applies to CYP2A2, CYP2C13 and CYP3A18. Class I also includes 'female' CYP2C12 isoform (steroid sulfate 15 $\alpha$ -hydroxylase), whose expression is similar in young rats of both sexes. However, in the progress of the sexual maturation the expression increases in females, whereas it is totally inhibited in males. The representative of class II is CYP3A2, whose expression in males occurs after reaching sexual maturation, whereas in females it is subject to selective suppression. In addition to the sex-specific isoforms, there are also isoforms which exist in both sexes, however they decisively prevail in one of them after reaching maturation. For example, in the liver of adult female rats the 'prevailing' isoforms are: CYP2C7, CYP3A9 and CYP2A1, because their expression is 3-10 times higher than in males. The best known model of sex-dependent hormonal regulation of cytochrome P450 expression is CYP2C11/12 expression in the rodent's liver. It is believed that similar regulatory mechanisms are responsible for sexual dimorphism of human cytochromes P450, such as CYP3A4, CYP1A2 and CYP2E1, however, this dimorphism is much less expressed (Scandlyn et al., 2008).

GH activates several signaling pathways of potential importance for the regulation of CYP expression. In females one of them is the cascade of arachidonic acid triggered by activated phospholipase A2 and enhanced by Ca<sup>2+</sup> influx into the cell. As a result, it comes to CYP-dependent production of epoxide derivatives of arachidonic acid, which increases CYP2C12 expression (Gonzalez & Lee, 1996). In the liver, the key regulator of the GH-dependent cytochrome P450 gene expression is STAT5b transcription factor being a representative of STAT protein family (Buitenhuis et al., 2004). In male rats, in the period between GH pulsations, the STAT5b activity is negligible or undetectable. In females the continuous profile of GH secretion causes its constant activation at low, but detectable level. STAT5b, together with STAT5a, can activate CYP2C12 gene expression by binding sequences, which

are unavailable in males (Tannenbaum et al., 2001). STAT5b contains sulfhydryl groups so it can bind to cytoplasmic domain of the GHR and undergo phosphorylation through the active GHR-JAK2 complex. Subsequently, STAT undergoes dimerization and then rapid translocation to the nucleus, where it activates transcription of target genes. It can regulate the expression of CYP genes directly, by binding their promoter sequences, or indirectly, by co-activation or co-repression of other transcription factors genes, which play the role of primary target (Lobie & Waxman, 2003). STAT5b has an influence to epigenetic regulatory mechanisms as well. It activates the genes silenced as a result of methylation, and strengthens the local conversion of chromatin to the transcriptionally active form (Waxman & O'Connor, 2006). On the other hand, it can inhibit binding of hepatocyte nuclear factors to CYP2C12 gene promoter. STAT5b is able to bind with the receptors of vitamin A derivatives, e.g. with retinoic acid receptor (RAR), however, it is not yet known if it is relevant in the hormone-dependent regulation of cytochrome P450. In the acute promyelocytic leukaemia, a fusion protein STAT5b-RAR $\alpha$  has been described. It binds to RARE sequences both as a STAT5b-RAR $\alpha$ /STAT5b-RAR $\alpha$  homodimer and STAT5b-RAR $\alpha$ /RXR heterodimer and inhibits the transcriptional activity of RAR $\alpha$ /RXR $\alpha$  heterodimer (Dong & Tweardy, 2002).

In the process of the regulation of CYP gene expression, STAT proteins cooperate mostly with hepatocyte nuclear factors - HNFs (Park et al., 2006). HNFs representing this superfamily of proteins, such as HNF-1 $\alpha$ , HNF-4 $\alpha$ , HNF-3 $\gamma$ , HNF-3 $\beta$  and HNF-6, exist mainly in the liver. Some of them, e.g. HNF-6, are directly regulated by GH (Wauthier & Waxman, 2008). They take part in the differentiation of hepatocytes and regulation of gene expression associated with the fundamental metabolic pathways in the liver: glycolysis, gluconeogenesis, and the metabolism of lipoproteins, fatty acids and bile acids (Gonzalez, 2008). HNFs bind to DNA sequences as monomers, homodimers or RXR heterodimers.

A key role in the aspect of the sex-differentiated expression of hepatic proteins plays HNF-4 $\alpha$ , binding GTTAAT sequence in target genes. HNF-3 $\beta$  and HNF-6 factors are the positive regulators of 'female' expression of CYP2C12 and the negative regulators of 'male' expression of CYP2C2, induced, in turn, by HNF-4 $\alpha$  and HNF-3 $\gamma$ . In mice, HNF-4 $\alpha$  is responsible for female-specific expression of Cyp3a41. Sex differences in the structure of chromatin - higher methylation and acetylation of respective binding sites in females, underlie this process (Bhadhprasit et al., 2011). HNF-4 $\alpha$  is essential for the proper induction of CYP genes with participation of PXR (CYP2C9, CYP3A4) and CAR (CYP2C9) receptors (Tamási et al., 2011). It appeared that in humans, microRNA: miR-24 and miR-34a are responsible for the negative regulation of HNF-4 $\alpha$  by degradation of its mRNA by miRNA/RISC complex (*RNA-induced Silencing Complex*) and/or translational repression (Takagi et al., 2010). Down-regulation of HNF-4 $\alpha$  reduces the expression of CYP7A1 and CYP8B1 involved in the synthesis of bile acids. Because miR-24 and miR-34a are regulated by oxidative stress, it is considered that they play a negative role in the pathogenesis of liver diseases (Takagi et al., 2010). The fact that the natural HNF-4 $\alpha$  ligand is linolenic acid, suggests the possibility of regulating its activity by the diet and pharmacological modulation (Gonzalez, 2008; Hwang-Verslues & Sladek, 2010; Jover et al., 2009).

GHNF (*Growth Hormone-regulated liver Nuclear Factor*) is another transcriptional factor regulated by GH, 'dominant' in females and having five binding sites in CYP2C12 gene promoter (Waxman et al., 1996). In turn, GABP (*GA-binding Protein*) is a protein, binding

DNA sequences rich in guanine and adenine. It is associated with sex-dependent regulation of CYP genes on the epigenetic level. Demethylation of CpG (*Cytosine-phosphate-Guanosine*) islands existing within the promoters of different genes allows binding of GABP and their transactivation (Waxman & O'Connor, 2006). Moreover, the representatives of Rsl (*Regulators of sex-limited proteins*) protein family – KRAB (*Krüppel-associated Box*) proteins, through the stabilization of the transcriptionally inactive heterochromatin, act as transcription repressors of genes specific to males in the liver of adult female rodents (Krebs et al., 2003).

#### 4. Regulation of cytochrome P450 gene expression by other signaling pathways

In addition to already described factors, in the regulation of cytochrome P450 gene expression are involved numerous intracellular signaling cascades, until recently, not connected with this function. Among them are signaling pathways dependent on NF- $\kappa$ B, MAP kinases, and  $\beta$ -catenin (Braeuning, 2009; Murray et al., 2010; Zordoky & El-Kadi, 2009). Glucocorticoid receptor and GATA4, Nrf2 and C/EBP transcription factors also play important role in the transcriptional regulation of cytochromes P450 (Dvorak & Pavek, 2010; Jover et al., 2009; Mwinyi et al., 2010a; Yokota et al., 2011). It can not be excluded that there are significant functional dependencies allowing for the hormonal control of the mentioned signaling pathways. It is known that GH, the main hormone supervising CYP expression, directly regulates the gene of Nfkbiz (*Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta*), the inhibitor of transcription factor NF- $\kappa$ B (Wauthier & Waxman, 2008). In addition, the phenomenon of cross-talk was confirmed between the nuclear receptors of xenobiotics and multimodal transcription factors like glucocorticoid receptor and NF- $\kappa$ B (Dvorak & Pavek, 2010; Zordoky & El-Kadi, 2009).

NF- $\kappa$ B is a pleiotropic transcription factor, which regulates over 200 genes related to, among others, the immune response, apoptosis, osteoclastogenesis, and inflammatory processes (Zordoky & El-Kadi, 2009). Classical (canonical) NF- $\kappa$ B signaling pathway is the phosphorylation and subsequent degradation of I $\kappa$ B (*Inhibitory kappa B protein*) - cytoplasmic protein inhibiting translocation of NF- $\kappa$ B factor to the nucleus – by the activated I- $\kappa$ B kinase - IKK (*Inhibitory Kappa B protein Kinase*). The released NF- $\kappa$ B may bind to the corresponding DNA sequences in the nucleus. Three mechanisms regulating cytochrome P450 expression and activity, with the participation of NF- $\kappa$ B have been proposed: direct, by binding to promoter sequences of CYP1A1, CYP2B1/2, CYP2C11, CYP2D5, CYP2E1, CYP3A7 and CYP27B1 genes; indirect, through repression of receptors, such as AhR, CAR, GR, PXR, RXR, PPAR, FXR, and LXR; and by post-translational regulation including induction of heme oxygenase and/or an impact on the stability of CYP proteins (Willson & Kliewer, 2002; Zordoky & El-Kadi, 2009).

Growing evidence indicates that MAP kinases participate in regulating the expression of drug metabolizing enzymes of phase I and II (Murray et al., 2010). MAPK activators: sorbitol and EGF (*Epidermal Growth Factor*) inhibit constitutive and induced expression of CYP isoforms, however anisomycin does not cause such an effect or shows a weak stimulation effect (Bachleda et al., 2009). MAP kinases catalyze the phosphorylation of the complexes formed with the participation of transcription factors, including nuclear receptors, cytoplasmic receptors of AhR type and members of the AP-1 family (c-Fos, c-Jun), and

because of that, they may affect their ability to transactivate target genes (Braeuning, 2009; Murray et al., 2010). MAPK-dependent pathways are crucial for regulating proliferation and differentiation of cells and their response to stress factors, exposure to chemicals present in the environment, and radiation (Murray et al., 2010). Activation of MAPKs by pro-inflammatory cytokines causes, among others, phosphorylation of JNK (*c-Jun N-terminus Kinase*) kinase, which in turn phosphorylates HNF-4 $\alpha$  and inhibits transactivation of CYP7A1 and CYP8B1 genes (Riddick et al., 2004). In this way, MAPKs are involved in the feedback inhibition of CYP genes participating in the metabolism of endobiotics.

In the liver, drug metabolizing enzymes are characterized by zonal distribution with the predominance of expression in the perivenous zone (Braeuning & Schwarz, 2010a). EGF/Ras/MAPK and WNT/ $\beta$ -catenin/TCF signaling pathways participate in the regulation of such gene expression (Braeuning, 2009; Braeuning & Schwarz, 2010a). A model of antagonistic relationship between these pathways has been proposed: Ras-dependent pathway promotes the expression of genes in periportal zone (so called zone 1), whereas  $\beta$ -catenin-dependent pathway promotes expression in pericentral zone (zone 3), of liver acinus (Braeuning, 2009). This applies not only to genes encoding CYP apoprotein, but also to genes involved in heme biosynthesis, which is the prosthetic group of these enzymes (Braeuning & Schwarz, 2010b). Studies in a mouse model showed that  $\beta$ -catenin cooperates with AhR, activating a constitutive CYP1A1 expression and increasing its induction by AhR ligands, through strengthening AhR potential for transactivation (Braeuning et al., 2011).

Glucocorticoid receptor (GR) is involved in the regulation of cytochrome P450 expression, through at least three mechanisms: direct binding of GR to specific promoter sequences called glucocorticoid response elements (GREs); indirect binding of GR to specific promoter sequences as a component of the multiprotein complex; and up or down-regulation of other transcription factors, AhR, or nuclear receptors: PXR, CAR and RXR. The final effect of glucocorticoids on CYP gene transcription is usually the result of several mechanisms (Dvorak & Pavek, 2010; Monostory et al., 2009).

GATA proteins belong to the group of transcription factors containing 'zinc finger domains', which recognize the DNA motif (A/T)GATA(A/G). They regulate the process of embryogenesis, especially heart development and the expression of detoxification enzymes and transporters. Binding sites of GATA-4, a main GATA protein in the liver, are located, among others, in the CYP2C19 and CYP2C9 gene. GATA-dependent expression is regulated by specific co-regulators, e.g. GATA-4-dependent activation of CYP2C19 gene transcription is inhibited by FOG-2 (*Friend of GATA-2*) (Mwinyi et al., 2010a, 2010b).

Transcription factor Nrf2 (*Nuclear factor-erythroid 2-related factor* or *NFE2-related factor 2*) is probably one of the main regulators of the antioxidant response (Nguyen et al., 2009). It belongs to the group of factors characterized by bZIP (*basic-leucine Zipper*) structure. It mostly regulates the expression of phase II enzymes of xenobiotic metabolism and phase III membrane-bound transporters, but it is also associated with the regulation of CYP2A5 and CYP2A6 genes through StRE (*Stress Response Elements*) and ARE (*Antioxidant Response Elements*) sequences (Abu-Bakar et al., 2007; Yokota et al., 2011). It has been suggested that there is interference between Nrf2 and other receptors regulating the expression of cytochrome P450, e.g. AhR, LXR and FXR. This may be important for individual susceptibility to the development of diseases, including lung cancer (Anttila et al., 2010; Kay et al., 2011).

C/EBP proteins (*CCAAT/Enhancer Binding Protein*) are transcription factors belonging to the group of LETF factors (*Liver-Enriched Transcription Factors*). They bind to CCAAT regulatory sequence and TT/GNNGA/CAAT enhancer sequence (Ramji & Foka, 2002; Rodríguez-Antona et al., 2003). Just as Nrf2, they have a characteristic C-terminal domain responsible for DNA binding, characterized by the structure of basic-leucine zipper. C/EBP may participate in the transcriptional regulation of some cytochrome P450 genes, such as CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP3A4, CYP3A5 and CYP3A7 (Pitarque et al., 2005). In hepatocytes, this regulation takes place in cooperation with HNFs and other transcription factors. C/EBP $\alpha$  and HNF-3 $\gamma$  regulate CYP3A4 gene expression probably by chromatin remodeling (Rodríguez-Antona et al., 2003).

## 5. Clinical implications

Practical applications of the knowledge about signaling pathways regulating cytochrome P450 gene transcription are very attractive in the context of protection the body from the potential harmful action of xenobiotics and drugs, and retention of pathophysiological processes. Nuclear receptors important for transactivation of CYP genes play a key role in the pathogenesis of many diseases - mainly of metabolic origin - and they may represent valid therapeutic targets for these disorders. Their role in liver diseases, including cholestatic and fatty liver disease, drug-induced hepatotoxicity, viral hepatitis, fibrosis and neoplastic hiperplasia is well understood (Wagner et al., 2011). In the kidneys they play an important role in the mechanism of nephropathy, especially diabetic, as they regulate the intensity of cellular infiltration, apoptosis, secretion of inflammatory cytokines, intensity of oxidative and nitrosative stress, secretion of prothrombotic growth factors, fatty acids synthesis, and the accumulation of cholesterol and triglycerides. VDR, FXR and PPARs seem to play the main role in these processes (Levi, 2011). VDR shows a nephroprotective action, among others, by inhibition or antagonism in respect of the renin-angiotensin-aldosterone system (RAAS) and the NF- $\kappa$ B signaling pathway (Deb et al., 2009; Zhang et al., 2010). FXR inhibits expression of SREBP-1 (*Sterol Regulatory Element-Binding Protein 1*) and ChREBP (*Carbohydrate Response Element-Binding Protein*), transcription factors that regulate gene expression of lipogenic and glycolytic enzymes, especially in the liver and adipose tissue (X. Wang et al., 2009). PPAR $\alpha$  regulates renal fatty acid  $\beta$ -oxidation, preventing at the same time the accumulation of lipids and lipotoxicity phenomenon, and also controls the formation of foam cells (Rigamonti et al., 2008).

Increasingly, attempts are being made to modulate the expression of nuclear receptors through the creation of specific ligands (Perez et al., 2011; Levi et al., 2011). Unfortunately, at the present stage it is impossible to determine the correlation between the structure of the ligand and physiological response. The administration of non-selective rexinoids increases triglycerides concentration (as the result of SREBP-1c transactivation by LXR/RXR), inhibits the thyroid axis and causes hepatomegaly. It is desirable therefore to develop rexinoids selective for PPAR $\gamma$ /RXR and LXR/RXR heterodimers, the so-called SNUuRMs (*Specific Nuclear Receptor Modulators*), acting differently than the known PPAR $\gamma$  and LXR ligands (Perez et al., 2011). In the treatment of autoimmune and neurodegenerative disorders, retinoids which are modulators of retinoic acid receptors can also be applied (Alvarez et al., 2011). Application of the agonists of: VDR (doxercalciferol), FXR (INT-747) and PPARs (fibrates) inhibits and even reverses the pathological changes observed in diabetic kidney

injury (Levi, 2011; Thomas et al., 2008). Agonistic and antagonistic RXR ligands could be used in the treatment of obesity, type 2 diabetes and insulin resistance, i.e. the components of metabolic syndrome (Levi, 2011; Perez et al., 2011).

Some of cytochrome P450 and transcription factors genes are hormone-dependent. Sex differences in the expression of early GH response genes may be responsible for gender differences in predisposition to certain diseases. For example, 29 of these genes, specific to male mice, is a target for the Mef2 transcription factor (*Myocyte enhancer factor 2*), whose activation in hepatic stellate cells is associated with the process of liver fibrosis and cirrhosis, increasing the male' risk of developing hepatocellular carcinoma (Wauthier et al., 2010). Progress of the studies on this phenomenon is necessary for rational drug administration, a good example of what can be attempt to clinical use of NF- $\kappa$ B inhibitors. Significant changes in cytochrome P450 expression and activity caused by the activation of NF- $\kappa$ B are found in the states, in which increased secretion of inflammatory mediators and the excessive oxidative stress can be observed, e.g.: inflammatory bowel diseases, rheumatoid arthritis, chronic exposure to stress, diabetes, kidney diseases, congenital heart diseases, or during aging (Zordoky & El-Kadi, 2009). NF- $\kappa$ B is now seen as a factor linking inflammatory process, oxidative stress and cancer with the metabolism of xenobiotics (Assenat et al., 2006). The inflammatory process accompanying cancers, may, through NF- $\kappa$ B, disturb CYP expression and thereby alter the effectiveness of chemotherapy.

In addition, the role of glucocorticoid receptor in the regulation of expression of cytochromes P450 such as CYP1A1 or CYP1A2, is extremely important for clinical practice. On one hand - the use of glucocorticoids as drugs is commonplace in medicine and has many side effects including not always conscious interactions of drug-drug type. On the other hand - CYP1A subfamily is the main group of cytochrome P450 responsible for bioactivation of xenobiotics and production of harmful and carcinogenic derivatives (Dvorak & Pavek, 2010; Monostory et al., 2009). That results in serious medical implications, namely changes in susceptibility to xenobiotics and in pharmacokinetics and pharmacodynamics of drugs, which must be taken into account by physicians and lead to the control of pharmacotherapy.

## 6. Conclusion

In recent years there has been significant progress within the meaning of the mechanisms regulating cytochrome P450 expression. It was found that the main role in the regulation of sex-specific CYP expression plays the growth hormone, the effects of which are dependent on daily secretion pattern, different in males and females. Disorders of intrinsic mechanisms controlling hormone secretion may lead to the modulation of CYP genes expression.

Both GH-dependent and GH-independent signal transduction is strictly connected with activation of numerous DNA-binding proteins. It has been described a number of new factors and signaling pathways involved directly or indirectly in the regulation of expression, primarily on the stage of transcription. The ligands for nuclear receptors previously known as orphan have been identified (receptors deorphanisation).

In addition, drug-metabolizing enzymes, xenobiotic transporters and their targets appear to be under the epigenetic control, hence separation of the new discipline called pharmacoeigenetics. Although the effects of epigenetic modifications on drug metabolism

were not examined extensively, they probably play an important role in determining the tissue-specific expression of CYP genes both in normal and cancer tissues. As a result, epigenetic modifiers may considerably alter the metabolism and/or disposition of many xenobiotics. Post-transcriptional regulation by microRNAs seems to be a key mechanism underlying the discrepancy between hepatic mRNA and protein expression of genes involved in drug metabolism.

Our knowledge of the regulatory mechanisms for cytochrome P450 expression represents the base of understanding the cross-talk between endobiotic and xenobiotic metabolism. On the other hand, there are large inter-individual variations in the expression of CYP genes in humans and the genotypic and phenotypic variability of the key regulators of the CYP gene transcription significantly influences individual response to xenobiotics, including drugs. A major future challenge will be to explain the role of co-activators and co-repressors of cytochrome P450 gene transcription into current pathogenic and therapeutic concepts for the diseases. More population-based studies should be conducted, because they may help physicians predicting the results of therapy and adverse drug effects, including drug-drug interactions.

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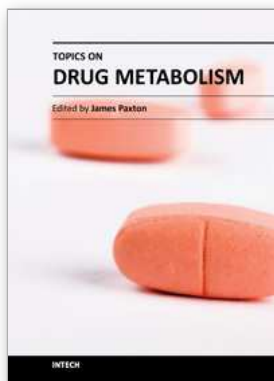


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In order to avoid late-stage drug failure due to factors such as undesirable metabolic instability, toxic metabolites, drug-drug interactions, and polymorphic metabolism, an enormous amount of effort has been expended by both the pharmaceutical industry and academia towards developing more powerful techniques and screening assays to identify the metabolic profiles and enzymes involved in drug metabolism. This book presents some in-depth reviews of selected topics in drug metabolism. Among the key topics covered are: the interplay between drug transport and metabolism in oral bioavailability; the influence of genetic and epigenetic factors on drug metabolism; impact of disease on transport and metabolism; and the use of novel microdosing techniques and novel LC/MS and genomic technologies to predict the metabolic parameters and profiles of potential new drug candidates.

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