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REVIEW

Role of xenobiotic metabolism in cancer: involvement of transcriptional and miRNA regulation of P450s

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Abstract Cytochrome P450 enzymes (P450s) are important targets in cancer, due to their role in xenobiotic metabolism. Since P450s are the "bridges" between the environment and our body, their function can be linked in many ways to carcinogenesis: they activate dietary and environmental components to ultimate carcinogens (i), the cancer tissue maintains its drug resistance with altered expression of P450s (ii), P450s metabolize (sometimes activate) drugs used for cancer treatment (iii) and they are potential targets for anticancer therapy (iiii). These highly polymorphic enzymes are regulated at multiple molecular levels. Regulation is as important as genetic difference in the existing individual variability in P450 activity. In this review, examples of the transcriptional (DNA methylation, histone modification, modulation by xenosensors) and post-transcriptional (miRNA) regulation will be presented and thereby introduce potential molecular targets at which the metabolism of anticancer drugs, the elimination of cancerogenes or the progress of carcinogenesis could be affected.

Keywords Drug metabolism · P450 · AHR · CAR · PXR · MiRNA

Abbreviations

ADPF	AHR degradation promoting factor
AHR	Aromatic hydrocarbon receptor
AHRR	Aromatic hydrocarbon receptor repressor
ARNT	Aromatic hydrocarbon receptor nuclear translocator
ARE	Antioxidant response element
ASC2	Activating signal cointegrator 2
B[*a*]P	Benzo[a]pyrene
CAR	Constitutive androstane receptor
CREBBP	CREB-binding protein
DNMT	DNA methyltransferase
ER	Estrogen receptor
FOXO	Forkhead box O
GR	Glucocorticoid receptor
GRIP1	Glucocorticoid receptor interacting protein 1
HDAC1	Histone deacetylase-1
HIF-1	Hypoxia induced factor
HNF-4α	Hepatocyte nuclear factor
KEAP-1	Kelch-like ECH-associated protein 1
3-MC	3-Methylcholantrene
NcoR	Nuclear receptor corepressor
NF-κb	Nuclear factor kappa-light-chain-enhancer of activated B cells
NRF2	NF-E2-related factor 2
PRMT1	Arginine methyltransferase 1
PXR	Pregnane X receptor
RXR	Retinoid X receptor

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SMC-1	Structural maintenance of chromosomes 1-like 1
SRC-1	Steroid receptor coactivator-1
SMRT	Silencing mediator for retinoid and thyroid receptor
TUF2	Transcriptional intermediary factor 2
VDR	Vitamin D receptor
XAP2	Immunophillin like X protein XAP2
XAR	Xenobiotic activated receptors

Introduction

The human body is exposed to a wide range of external chemicals; both purposely (e.g., medicines) and accidentally (e.g., environmental contaminants) and these foreign molecules (xenobiotics) are metabolized by enzymes called cytochrome P450s (P450). P450s are heme-thiolate enzymes that participate in the biotransformation of xenobiotics and production of many important endogenous compounds including steroid hormones, prostaglandins, and leukotrienes [1, 2]. Their expression is believed to be highly regulated; some P450s are expressed only in specific tissues and at times in specific cells within the tissue. Similarly, the expression pattern of a number of P450s is different at each developmental stage and different in females and males. Paradoxically, these enzymes catalyze the formation of reactive intermediates of thousands of chemicals that can damage DNA, as well as lipids and proteins. P450 expression can also affect the production of proliferation-promoting molecules derived from arachidonic acid, and alters various downstream signal-transduction pathways. Reactive intermediates, activated carcinogens, and arachidonic acid derivatives can be precursors to malignancy and cause chemical cancer [3]. In a developed cancer, these enzymes can determine the outcome of anticancer therapy and altered expression of P450s can support cancer progression and cause drug resistance [4, 5].

Since P450s are the "bridges" between the environment and our body, their function can be linked in many ways to carcinogenesis: they activate xenobiotics to ultimate carcinogens but at the same time they metabolize (and in some cases activate) drugs used for cancer treatment (Table 1). In some tumors, the cancer tissue maintains its drug resistance with altered expression of P450s and this explains why they are potential targets for anticancer therapy. Mostly, dose P450s could be linked to chemical cancer, which are involved in xenobiotic metabolism (CYP1-4 family), and their regulation is discussed in the following sections.

Until the last decade, it was thought that genetic polymorphism of cancer-related genes is responsible for tumor development. New findings of epigenetics and signal transduction suggest that during carcinogenesis, these factors (e.g., chromatin conformation, regulatory mechanisms) are as important as the genetic background.

There are many published reviews discussing the epigenetics of P450s and their role in cancer [3, 6, 7] and there are many introducing the function of nuclear receptors in this disease [8–10].

In the present manuscript, both regulation types—transcriptional and miRNA regulation mechanisms—were described from an aspect of xenobiotic metabolizing P450s and their role in cancer. In the past it was thought that mainly genetic polymorphisms were due to the variation of P450 activities and some genotypes increase the risk of cancer. With this review we would like to highlight the importance of regulatory mechanisms in cancer, which harmonize the genetically determined P450 activity with the environmental effects and could be beneficially altered by anticancer drugs in the future.

Molecular aspects of p450 regulation

Transcriptional regulation

Cancer is a complex disease where genetics, lifestyle, and environment play important roles in dictating susceptibility to the disease. Environmental factors are transmitted to the cell by different regulatory mechanisms. Although the major regulation of P450s through xenosensors, nuclear receptors have been well studied. We provide an overview of new results in the field related to regulation by DNA methylation and histone modulation, since they are topics of considerable current interest, which may describe the large variation in expression seen for several important P450s in cancer.

DNA methylation

In mammals, the majority of CpG pairs are chemically modified by the covalent attachment of a methyl group to the C_5 position of the cytosine ring. DNA methylation occurs predominantly at CpG sites in the mammalian genome [11] by the DNA methyltransferase (DNMT) enzymes [12]. Methylation of DNA is regarded as a means of regulating gene expression through two general mechanisms. First, DNA methylation of gene promoters may prevent the physical binding of some transcription factors to their DNA-binding sites [13]. Second, the transcriptional silencing capability of DNA methylation may occur via indirect mechanisms involving changes in chromatin

Table 1 Role of xenobiotic metabolism in cancer

Result of xenobiotic metabolism by P450s	Changes in P450 activity	
	Promotes carcinogenesis	Promotes anticancer effect
Carcinogen deactivation	No	Yes
Precarcinogen activation	Yes	No
Anticancer drug deactivation	Yes	No
Anticancer prodrug activation	No	Yes

conformation. There is extensive evidence to support a functional role for promoter-CGI methylation in transcriptional repression [14–16]. DNA methylation of CpG-rich promoters of some genes correlates with tissue-specific gene silencing [17, 18]. Tumors are often characterized by an imbalance in cytosine methylation having both hypomethylation and hypermethylation of various regions of the genome. To date, several studies show altered DNA methylation of P450s in cancer, mostly of those P450s, which are involved in the metabolism of endogenous compounds [6]. Examples of such regulation are shown in the following section.

CYP1A1 Both hypermethylation (less active CYP1A1, altered metabolism of carcinogens) and hypomethylation (more active enzyme, higher activation of precarcinogens) of *CYP1A1* promotes carcinogenesis.

In prostate cells, CpG islands in CYP1A1 show segmented/selective methylation patterns; CpG sites from 1 to 36 are not methylated; this DNA region contains the *CYP1A1* promoter and is responsible for correct initiation of gene transcription, CpG sites 37 to 90, which corresponds to the *CYP1A1* enhancer region that mediates TCDD inducibility, exhibits cancer cell-dependent hypermethylation, and CpG sites 91 to 125 are commonly methylated, but no known regulatory function has been associated with this DNA region, possibly due to its positive methylation status [19]. In noncancerous prostate tissue, *CYP1A1* enhancer methylation could not be detected, but in prostate tumors, 36% (11 of 30) of the DNA samples was methylated (Table 2).

Environmental factors such as tobacco smoke have been shown to influence the DNA methylation of CYP1A1. Smokers' DNA was hypomethylated compared to nonsmokers on the upstream regions, containing functional XREs. In addition, there was an inverse correlation between methylation and the number of cigarettes smoked daily. Cessation of smoking results in the methylation of *CYP1A1* promoter being increased at 1–7 days after the last cigarette [20]. Although there was no correlation between EROD activity and the percentage of methylated DNA in a sample in either smokers or nonsmokers, a decrease in methylation caused significant higher CYP1A1 activity. A high inducibility of CYP1A1 has been connected with increased susceptibility to smoking-associated lung cancer [21, 22].

CYP1B1 CYP1B1 is overexpressed in a variety of human tumor cells such as the lung, breast, liver, gastrointestinal tract, and ovarian cancer [23, 24]. *CYP2B1* may be an important tumor marker because it hydroxylates estrogens and activates many procarcinogens. CYP1B1 enzyme could be methylated both on the promoter and on the enhancer of the gene. The promoter region contains the CpG sites of the core promoter region including SP1-binding sites and the enhancer region including AHR/ARNT-binding sites DRE2 and DRE3. Aberrant methylation in the CYP1B1 gene affects binding of transcription factors and enhancer molecules. In cancer, the methylation of this region is differently altered, depending on the type and original tissue of the tumor. Tokizane et al. [25] showed that increased *CYP1B1* expression in clinical

Table 2 CpG islands found in various P450 enzymes and their role of cancer

P450	CPG islands				
	Region	Methylation status	Consequences in activity	Tissue/cell line	References
CYP1A1	Enhancer/promoter	Hypermethylated	↓	Prostate cancer	[19]
	Enhancer/promoter	Hypomethylated	↑	Lung of smokers	[20]
CYP1B1	Enhancer/promoter	Hypomethylated	↑	Prostate cancer	[25]
	Enhancer/promoter	Hypermethylated	↓	Colorectal cancer	[26]
CYP2E1	Region not described	Hypomethylated	↓	Lung tumor	[31]
CYP2W1	I. exon/I. intron	Hypermethylated	↓	Colon cancer	[35–37]
CYP3A4	Enhancer/promoter	Hypomethylated	↑	HepG2	[38]

prostate cancer tissues is caused by hypomethylation both of the promoter and enhancer regions of the *CYP1B1* gene.

The same methylation pattern as in prostate cancer was observed in other cancers, for example, colorectal cancer. Here, inhibited activity of CYP1B1 was observed due to complete hypermethylation of the promoter region [26]. Because expression of *CYP1B1* is regulated by the methylation of its promoter/enhancer, this region may be a useful target for anticancer drugs and in preventive medicine (Table 2).

CYP2E1 Methylation of the CYP2E1 gene inhibits the expression of this enzyme in prenatal period [27]. In adult tissues, the methylation pattern of the CYP2E1 gene differs among various tissue types such as lung, kidney, placenta, liver, and skin, indicating that DNA methylation results in tissue-specific regulation [28, 29]. CYP2E1 metabolizes ethanol to its carcinogenic metabolite acetaldehyde and it is involved in the bioactivation of other small-molecule precarcinogens [30]. In lung tumors, lower methylation was observed and hypomethylation has been associated with underexpression of the *CYP2E1* gene [31].

CYP2W1 This enzyme has been shown to metabolize arachidonic acid and benzphetamine, as well as being able to metabolically activate several procarcinogens, including polycyclic aromatic hydrocarbon dihydrodiols, aflatoxin B1, or sterigmatocystin. *CYP2W1* is expressed at relatively low levels (mRNA) in the human adult non-transformed tissues, whereas the expression in colorectal cancer tissues was significantly higher (both at mRNA and protein levels) [32–34]. This suggests that the extent of *CYP2W1* expression in colorectal cancers might be a prognostic marker for malignancy and survival (Edler et al. 2009). CYP2W1 gene expression appears to be governed by gene methylation. The CYP2W1 gene was shown to contain one functional CpG island in the exon 1-intron 1 region, which was methylated in cell lines lacking *CYP2W1* expression, but unmethylated in cells expressing *CYP2W1* [35–37].

CYP3A A different DNA methylation pattern was found between primary hepatocytes and hepatocyte cell lines. HepG2 cells exhibit many cellular features of normal human hepatocytes, but also display characteristics resembling those of a cancerous or fetal hepatocyte. *CYP3A* expression in untreated HepG2 cells is fairly low, suggesting that their expression is reduced in these partially dedifferentiated cells. Dannenberg and coworkers were interested in determining whether CYP3A genes are regulated by DNA methylation in HepG2 cells. Their microarray experiments showed that after 5-aza-dC treatment (5-aza-2′-deoxycytidine, methylation inhibitor), expression of CYP3A4, CYP3A5, and CYP3A7 was two- to fourfold higher, suggesting a regulatory role of methylation with these P450s. The mentioned increase in expression was confirmed by real-time RT–PCR only for *CYP3A7* [38]. Since the CYP3A enzyme catalyzes the transformation of many drugs, understanding its regulation would open new possibilities in cancer therapy.

Histone modification

Post-translational modifications such as phosphorylation, acetylation, methylation, and ubiquitination on the N-termini of histones have been shown to play critical roles in gene regulation [39]. It is believed that the combination of modifications of the chromatin-associated histone and non-histone proteins and the interplay between these modifications create a marking system ("histone code"), which is part of the epigenetic mechanism for gene regulation [40]. The modified histones and methylated DNA sequences may interact in a synergistic manner, including methyl-CpG binding protein, nuclear receptor corepressor (NCoR), associated histone deacetylases, and histone methyl transferases, to regulate gene expression [41]. There are already several indicators of an association between histone-modifying enzymes and cancer [42]. Histone modifications are involved in the regulation of the two cancer-related P450s: CYP1A and CYP3A4.

Chromatin structure has been suggested to play an essential role in *CYP1A1* transcription. In the basal state, HDAC1 is bound to the CYP1A1 promoter and is released in concert with the recruitment of p300 upon B[*a*]P ligand activation of the receptor. HDAC1 removal allows for several histone-modification steps associated with the AHR-mediated induction of CYP1A1 expression. Removal of HDAC1 is necessary, but it is not sufficient to activate CYP1A1 expression [43]. CYP3A4 transcription is also regulated by a histone methyltransferase enzyme called protein arginine methyltransferase 1 (PRMT1). PRMT1 is required for the transcriptional activity of PXR. It is recruited to the 5′-region of the CYP3A4 gene to methylate histone H4 as a response to the PXR agonist rifampicin [44]. CYP3A4 is also regulated with PXR and is regulated by CAR albeit it at a lower rate of expression. Assenat and coworkers reported that the synthetic glucocorticoid, dexamethasone, induces histone H4 acetylation at the proximal CAR promoter region, and indirectly affects CYP3A4 induction by regulating CAR expression [45]. Interestingly, experiments for H4 acetylation on PXR promoter were not performed.

Regulation with xenosensors

A specific group of transcription factors and receptors that are specialized to regulate genomic processes to protect the

body against the innumerable chemicals found in the environment are called xenobiotic-activated receptors (XARs) or xenosensors. XARs regulate xenobiotic metabolism and disposition by controlling the expression and induction of drug-metabolizing enzymes and transporters. As the primary means of xenobiotic sensing and defense, XARs are intimately involved in drug disposition, polymorphic drug clearance, drug–drug interaction, and pathogenesis of some chemically induced diseases such as cancer. Furthermore, XARs integrate a broad range of protective mechanisms (such as antioxidative response and immune/inflammatory functions) to antagonize foreign chemicals [46]. Regulation of P450 expression has a high impact on both carcinogenesis (activation of precarcinogens, slow metabolism of toxic compounds) and on cancer therapy by anticancer drugs (narrows therapeutic index, a steep dose-toxicity curve).

The expression of P450s is primary regulated by two nuclear hormone receptor type xenosensors [8, 47–49], the constitutive androstane receptor (CAR), the pregnane X receptor (PXR), and two other type of xenosensors, namely the aryl hydrocarbon receptor (AHR) and nuclear factor (erythroid-derived 2)-like 2 (NRF2).

The prototype transcriptional circuit of an XARs for P450 induction is as follows: XARs are inactivated with associated proteins in the cytoplasm; binding with an agonist activates XARs; activated XAR translocates into the nucleus and heterodimerizes with a partner protein; and the XAR dimer binds to specific DNA sequences located in the enhancers of a battery of foreign-compound metabolizing genes. These receptors can alter the action of other nuclear receptors or transcription factors, thereby controlling the signaling pathways that regulate the homeostasis of bile acids, lipids, glucose, inflammation, vitamins, hormones, and others (Table 3).

Xenosensors are also able to crosstalk with other signalling pathways. The consequences of crosstalks are that the expression of a given battery of target genes that is expected to be regulated by a given signalling pathway in fact are dependent on the function of other signalling pathways as well. Given the multitude of biological partners with which xenosensors might interact, xenobiotic metabolism and its influence on carcinogenesis appear to be dependent on a very complex network of regulatory pathways. Some of the cancer-related crosstalks are listed in the following section with each xenosensor.

PXR Pregnane X receptor is one of the most frequent target receptors for xenobiotics and therefore its role in the regulation and control of drug metabolism is important to consider in relationship to drug-drug interactions. PXRs have been shown to be activated by various xenobiotics (e.g., rifampicin, clotrimazole, hyperforin), natural and synthetic steroids (e.g., 5ß-pregnane-3,20-dione, pregnenolone 16α-carbonitrile, dexamethasone, dehydroepiandrosterone), and bile acids (e.g., lithocholic acid and 6-keto lithocholic acid) [50]. After binding with the xenobiotic compound, PXR translocates to the nucleus and heterodimerizes with retinoid X receptor (RXR). The heterodimeric complex can bind to several responsive element types, such as direct repeats (DR-3, DR-4, and DR-5) and everted repeats (ER-6, ER-8) [51–53]. The modulation of basal activity and induction of transcriptional events are mediated by recruitment of coregulators: activators [SRC-1, SRC-2, SRC-3 (steroid receptor coactivator-1, 2 or 3), TUF2 (transcriptional intermediary factor 2), GRIP1 (glucocorticoid receptor interacting protein 1), CREBBP (CREB binding protein), AIB1 (amplified in breast cancer 1], or corepressors [NCoR (nuclear receptor corepressor), SMRT (silencing mediator for retinoid and thyroid receptor)] [54–58]. The signaling pathway is even more complex if the crosstalk mechanisms with other receptors are taken into consideration. Major interactions are summarized in Table 3 and described briefly below.

It has been observed that the expression of PXR in prostate, ovarian, and colon cancer cells can modulate tumor cell metabolism and sensitivity to several cytotoxins. For instance, PXR ligands such as rifampicin and hyperforin (the active constituent of the herbal antidepressant St. John's Wort) significantly enhance both the hepatic elimination of irinotecan in patients, and the intratumoral glucuronosylation and inactivation of the drug. Cyclophosphamide is widely used to treat a variety of cancers and it is activated mostly by CYP2B6 and CYP3A4 [59]. Treatment of hepatocytes with mentioned PXR inducers markedly increased hydroxylation of cyclophosphamide and its isomer ifosfamide [60]. Tamoxifen is mainly metabolized by CYP3A4, and at the same time, induces this enzyme [61], and with this, accelerates its own clearance as a result of autoinduction [62]. PXR and CYP3A4 is also activated by the microtubule stabilizing agent paclitaxel, but not with its structurally related molecule docetaxel. The mechanism behind the two structurally related drugs is as follows: paclitaxel stimulates the displacement of SMRT cofactor on the PXR/RXR complex while docetaxel does not [63]. In contrast to paclitaxel, cyclophosphamide, or tamoxifen, ecteinascidin (ET)-743 anticancer has been shown to inhibit the transcriptional activation of CYP3A4 by direct antagonizing PXR [64].

PXR and CAR Because PXR-responsive elements are recognized and transactivated by CAR and vice versa, PXR and CAR can activate the overlapping series of genes. In addition, these receptors compete for a common partner, RXRalpha; for common coactivators, such as SRC-1 and PGC-1alpha and for the same ligands [65–68], but there are

Table 3 Regulation of human P450s by XAR crosstalks

P450	Crosstalk	Consequences	References	Mechanisms
CYP1A	AHR and GR	↓	[113, 114]	Direct interaction of AHR and activated GR
	AHR and ER	↑	[118–120, 122]	ER coactivates AHR, ER interacts with AHR/ARNT complex
	AHR and HIF1	↓	[123, 124]	Sharing ARNT partner
	AHR and NRF2	↑	[138, 139]	Transactivating the same responsive element
CYP2B6	CAR and GR	↑	[101]	Direct interaction of CAR and GR, glucocorticoid responsive element (GRE) in CAR distal region
	CAR and FOXO	↑	[98, 99]	FOXO binds directly with CAR
	CAR and PXR	↑	[65–68, 70]	Transactivating the same responsive element
	PXR and VDR	↑	[72–74]	Transactivating the same responsive element
CYP2C9	CAR and HNF-4α	↑	[79]	Synergizing the effect of CAR
	PXR and HNF-4α	↑	[79]	Synergizing the effect of PXR
	PXR and VDR	↑	[72–74]	Transactivating the same responsive element
CYP2J2	NRF2 and c-Jun	↑	[144]	NRF2/c-Jun binds to the same responsive element as c-Jun/c-Jun
CYP2S1	AHR and HIF1	↑	[127]	AHR and HIF1 binds to the same responsive element
CYP3A4	PXR and CAR	↑	[65–68, 70]	Binding to the same responsive element
	PXR and VDR	↑	[72–74]	Transactivating the same responsive element
	PXR and GR	↑	[79]	Cofactor, facilitate the binding of PXR
	PXR and HNF4 α	↓	[79, 80]	Binding the same coactivators

differences in the degree to which specific genes are activated by either CAR or PXR agonists, which undoubtedly contribute to the distinct pharmacologies of xenobiotics. Retinoids that are used clinically to treat acute promyelocytic leukemia, skin cancer, Kaposi's sarcoma, and cutaneous T-cell lymphoma were shown to activate CYP3A4 mainly via CAR and not PXR. These findings suggest that retinoids may have complex and variable effects on xenobiotic responses in these patients [69].

PXR and VDR VDR mediates the effect of 1α, 25-dihydroxyvitamin D3, retinoids and carotenoids to genes that are involved in mineralization, epidermal development, etc. After binding the ligand, VDR/RXR form a heterodimer and then bind to and transactivate the vitamin D responsive elements (VDREs) that are present in the regulatory region of target genes [70]. Wang's experiments prove that certain retinoids and carotenoids transactivate the PXR/RXR-mediated pathway and upregulate CYP3A4 gene expression in a human hepatoma cell line [71]. VDR binds and activates other PXR/CAR-target genes such as CYP3A4, CYP2C9, and CYP2B6 [72–74]. Because vitamin D is a common component of food products and it is also produced in the skin, it is possible that its activating influence on P450s may contribute to some of the interindividual variations of these enzymes. Induction of CYP3A4 by VDR ligands could have importance in cancer prevention, since a higher level of CYP3A4 gives better protection in carcinogen deactivation or in cancer therapy, and faster activation of anticancer prodrugs [75].

PXR and GR Dexamethasone was shown to induce CYP3A4 transcription in primary human hepatocytes [76], suggesting a functional cross talk between PXR and GR (glucocorticoid receptor). The cross talk potentially regulates metabolism of steroid hormone and sterol homeostasis. Induction of CYP2B6 by PXR is also augmented by dexamethasone, suggesting that GR regulates PXR expression. Besides modulating PXR expression, activated GR (but not the receptor alone) acts as a cofactor to facilitate the binding of PXR to CYP2B6 [77]. Based on these findings, active GR can serve as an enhancer in the induction of the CYP2B6 gene and this could be useful in cancer therapy. Ketoconazole and miconazole, which were identified as GR antagonists [78], can block the effect of GR, and treatment with these imidazole derivatives might improve the pharmacokinetic properties of some CYP2B6 dependent, anticancer drugs (for example paclitaxel and tamoxifen).

PXR and HNF-4α PXR/HNF-4α crosstalk is characterized as an enhancer as well as regulator of constitutive expression of P450s. CYP2C9 has many anticancer substrates (e.g., cyclophosphamide, ifosfamide, or tamoxifen) and it is regulated by both CAR and PXR. Additionally, two proximal HNF-4α-binding sites functionally control the transcriptional activation of CYP2C9. HNF-4α synergizes with PXR or CAR to enhance promoter activity of *CYP2C9* and HNF-4α sites are essential for maximal induction of CYP2C9 promoter [79]. Recent studies for *CYP3A4* indicate that a distant enhancer module containing a PXR response element (F-ER6) is a recognized binding

site for HNF-4α [80]. This element supports constitutive expression of CYP3A4. The applications of drugs that target these interactions with PXR will continue to be a focus of research in cancer prevention in the future.

CAR In addition to the pregnane X receptor (PXR, NR1I2), the constitutive androstane receptor (CAR, NR1I3) is the other nuclear receptor that plays a role in the transcriptional activation of P450 genes after exposure to anticancer drugs (e.g., tamoxifen, cyclophosphamide, ifosfamide). CAR is constitutively active without ligand, and many xenobiotics (phenobarbital and phenytoin) act primarily by causing its nuclear translocation rather than serving as ligands [81, 82].

Induction of many P450s, like the CYP2B6, CYP2C9, CYP2C8, and CYP2C19 is mediated with the nuclear receptor CAR. Phenobarbital-type CYP2B6 inducers activate LKB1 (serine/threonine kinase 11), which can phosphorylate AMPK in human hepatocytes and LMH cells [83, 84]. Activation of cytosolic CAR by AMPK results in its dissociation from chaperone partners, such as cytoplasmic CAR retention protein (CCRP) and HSP90. Translocation of CAR to the nucleus, presumably dependent on the activity of the protein phosphatase PP2A, is followed by association with the retinoid X receptor (RXR) and binding to the PBREM (phenobarbital responsive enhancer module). Transcriptional activation occurs upon CAR binding to the PBREM, which contains two nuclear receptor DR4 sites (NR1 and NR2). CAR coactivators identified to date that facilitate transactivation include GRIP1/TIF2, peroxisome proliferator-activated receptor-γ coactivator (PGC-1γ), SRC-1, Sp1, activating signal cointegrator 2 (ASC-2) and more recently, structural maintenance of chromosomes 1-like 1 (SMC-1) [85–90]. Modulating CAR activity could be useful to adjust metabolism of some cancer-related drugs.

It was reported that CYP bioactivates anti-cancer prodrug ifosfamide [9] in breast cancers and that the expression of CYPs including *CYP2B6* was lower in the tumor tissue than in the adjacent normal tissue [91, 92]. Coadministration of phenytoin (CAR activator) in an anticancer therapy has been reported to decrease the level of the prodrug cyclophosphamide and increase the plasma levels of its cytotoxic metabolite 4-hydroxycyclophosphamide through the hepatic induction of CYP2B6 and CYP3A4. The problem is, that at the same time, induced CAR increases cancer cell resistance to 4-hydroxycyclophosphamide by increasing the detoxification rate of this compound.

CAR and PXR could serve as carcinogenesis promoters; it has been proposed that they directly affect tumor growth by controlling the expression of genes involved in motility, apoptosis, and cell–cycle progression in cancer cells [93–95]. *CYP2B6* mRNA was also diminished in hepatocellular carcinoma with venous invasion but not in hepatocellular carcinoma without venous invasion [96]. Also, testosterone metabolizer CYP2B6 was found to decrease in prostate cancer. Decreased expression of CYP2B6 significantly correlated with faster cancer progression and poor prognosis in human prostate cancer. These findings suggest that CYP2B6 expression may be decreased in hormonal cancers, where the hormone is closely related to substrates of CYP2B6.

CAR and FOXO1 Forkhead box O (FOXO) transcription factors play an important role in modulating metabolic functions. When nutrient and insulin levels are low, FOXO1 promotes expression of gluconeogenic enzymes and its level is also higher in diabetic patients [97]. It is known that diabetes elevates the activity of hepatic drug metabolism in humans [98]. During the last decade, many scientific groups wanted to resolve the molecular connection between insulin regulation and drug metabolism. As a result, information on potential crosstalk between FOXO1 and xenobiotic metabolism was provided by Kodama and coworkers, who showed that FOXO1 binds to CAR and activates its transcriptional activity [99].

Increasing the level of P450s such as CYP2B6 or CYP3A4 in diabetes, increases production of sex hormones, leading to high plasma-free estrogen concentrations, which in turn activate the estrogen receptor (ER). Activation of these pathways can lead to proliferation, invasiveness, angiogenesis, and decreased apoptosis and will increase the chances of breast cancer in diabetic patients [100].

CAR and GR Although submicromolar concentrations of dexamethasone (DEX) are known to activate GR, it does not appear to induce CYP2B6 expression at the mRNA level [101] in primary hepatocytes. GR plays an indirect role in CYP2B6 regulation by inducing the expression of CAR itself. In huh7 cell transfection experiments, activated GR increased the constitutive activation of a CYP2B6-PBREM reporter construct by CAR alone, in the absence of inducers. In the presence of ligand activated GR, only PB treatment caused a further twofold CAR-mediated CYP2B6-PBREM activation, compared to control cells. These studies show that GR is involved synergistically in the xenobiotic-responsive regulation of human CYP2B6 by CAR [102]. Increasing CAR levels with GR agonists, such as imidazole derivatives would increase the level of CAR-dependent drug metabolism, which could be beneficial in certain cancer diseases.

CAR and HNF-4α. See PXR and HNF-4

CAR and VDR $1\alpha,25\text{-}(OH)_2D_3$ induces the expression of the CYP2B6, CYP2C9, and CYP3A4 in primary human

hepatocytes. The induction is mediated by VDR receptor, which binds to the same transactivating responsive elements (ER6, DR3, and DR4) shown to be targeted by PXR (see PXR/VDR cross talk) or CAR [103]. Since VDR activation increases CAR target P450s and with this its metabolic capacity, it could be established that VDR activators can serve as protectors from toxic compounds, which are inactivated by these enzymes, and on the other hand, vitamin D coadministration can increase the level of enzymes involved in anticancer drug activation.

CAR and PXR (see chapter PXR)

AHR The induction of *CYP1* family is mediated mainly through a specific cytosolic receptor, the aryl hydrocarbon receptor (AHR) [104]. Although AHR has long been recognized as a ligand-induced transcription factor, which is responsible for the xenobiotic activating pathway of several phase I and phase II metabolizing enzymes, recent evidence suggests that the AHR is involved in various cell signaling pathways critical to cell cycle regulation and normal homeostasis. Dysregulation of these pathways is implicated in tumor progression [105]. AHR not only mediates tumor promotion but also plays a role in tumor progression. It is also known that activation of the AHR may lead to deregulation of cell–cell contacts, thereby inducing unbalanced proliferation, dedifferentiation, and enhanced motility [106].

AHR exists as part of a cytosolic protein complex, which consists of two Hsp90 heat-shock proteins; a Hsp-90-interacting cochaperone p23 and an immunophillin-like protein (XAP2). In the presence of an exogenous ligand, like polycyclic aromatic hydrocarbons, anticancer drugs, e.g., docetaxel, erlotinib, tamoxifen, or dacarbazine), the receptor complex translocates to the nucleus, where it heterodimerizes with another protein, the aryl hydrocarbon nuclear translocator (ARNT). This heterodimer binds to consensus regulatory sequences termed AHREs (Aryl hydrocarbon responsive elements), XREs (Xenobiotic responsive elements) or DREs (Dioxin responsive elements), located in the promoter region of CYP1A1 and CYP1A2 and initiates their transcription [107]. The transcription of CYP1A1 is inhibited by the AHR-related factor aryl hydrocarbon receptor repressor (AHRR), which localizes in the nucleus in the form of a dimeric protein along with ARNT [108]. The AHRR/ARNT heterodimer acts as a repressor both by stopping transcription initiated at the XREs and by competing with AHR for heterodimer formation with ARNT. All AHR, ARNT, and AHRR proteins are members of the bHLH (basic helix-loop-helix) PAS (Per-ARNT-Sim) family of proteins. The bHLH motif is shared by other transcription factors such as MYC and MYOD and is the protein part essential for DNA binding of the AHR complex [109]. Heterodimerization of AHR/ARNT is facilitated by interactions between bHLP and PAS domains. Further interactions of the AHR/ARNT heterodimer with transcription factors such as Sp1 and NF-1 are essential to enhance the expression of the *CYP1A1* gene. The half-life of AHR depends on the regulated proteosomal degradation of AHR; AHR degradation is mediated by ADPF (AHR degradation promoting factor), which has been proposed to serve as an E3 ubiquitin ligase [110].

AHR and GR AHR has been shown to interact with the glucocorticoid receptor (GR) both in vitro and in vivo; GR decreases AHR-mediated expressions by interacting with XRE-binded AHR [111]. Decreased expression of P450s means prolonged half-life of some anticancer drugs or slower activation of procarcinogens. Recent evidence from studies in HepG2 cells and primary cultures of human hepatocytes has shown that dexamethasone reduces both basal and inducible CYP1A1 EROD activity. Furthermore, dexamethasone was shown to have direct effects on the modulation of TCDD-induced transcriptional activation as well as the proteosomal degradation of AHR in HepG2 cells. Induction of CYP1A1 protein by 3-methylcholantrene (3-MC) was also down-regulated by dexamethasone although it was not observed at the mRNA level [112]. These findings show that dexamethasone controls CYP1A1 expression in human hepatocytes and HepG2 cells through interactive regulatory crosstalk between GR and AHR receptors. The cross-reaction occurs only when both the AHR and GR are activated [113, 114]. In extrahepatic tissues, gefitinib and erlotinib antineoplastic drugs are metabolized by CYP1A1 and CYP1A2. Coadministration of the mentioned anti-GR imidazole-derivatives would prolong the drug exposure in the tumor [115].

AHR and ER Crosstalk of AHR and ARNT with the estrogen receptor α (ERα) has also been established in a number of different systems [116, 117] and could be important in estrogen-related cancers. TCDD does not bind to ERα, but it does inhibit ERα signaling. More importantly, ERα plays a significant role in modulating AHR activity; treatment of TCDD and E2 results in an increased induction of CYP1A1, compared to TCDD treatment alone. ERα has a direct interaction with the CYP1A1 promoter, suggesting that it acts as a coregulator of AHR-mediated transcriptional activation [118]. In human bronchial epithelial cells, ERα increased the basal mRNA levels of *CYP1B1* and the inducible protein levels of CYP1A1, thus regulating the expression of these genes at both the transcriptional and translational level, respectively [119]. A long time increase in CYP1 activity will lead to elevated concentration of free estrogen in the plasma, which in turn activates the ERα. Constant activation of ERα will promote

abnormal cell division and tumor growth. With this, AHR-ER crosstalk increases the chances for hormonal cancer. The interaction of ERβ with AHR and ARNT has also been demonstrated after 3-MC exposure [120].

ER- and AHR-signaling pathways have been demonstrated to share several coactivator proteins, such as SRC-1 and receptor-interacting protein 140 (RIP140) [121] and it is also known that AHR induces the proteasomal down-regulation of ER, which means that there are other cross points where these two receptors can interact and with this regulate CYP1A1 activity [122].

AHR and HIF1α Like AHR, HIF1α protein is a member of the PAS family and it also interacts with ARNT [123]. The fact that these proteins share the same dimerization partner suggests an interaction between these nuclear receptors.

During angiogenesis and tumor growth, HIF-1alpha dimerizes with ARNT, inducing expression of many genes, including vascular endothelial growth factor (VEGF).

In normal tissue, AHR sequesters ARNT, decreasing its interaction with HIF-1alpha and with that diminishing VEGF production. In many cancer tissues, increased VEGF is responsible for tumor growth and tumor vascularization. Stimulation of the AHR pathway with AHR inducers would enhance the sequestering effects of the AHR through interaction with ARNT and would inhibit carcinogenesis [124].

AHR/HIFα cross talk is important in the regulation of the human CYP2S1 enzyme. The function of *CYP2S1* is still unknown; very few studies report that this enzyme can process naphthalene type xenobiotics [125, 126]. This enzyme is regulated primarily by AHR, but a crosstalk between AHR and HIF-1α was also discovered after dioxin and hypoxia exposure, respectively [127]. Selective expression of *CYP2S1* in hypoxic tumors results from this crosstalk. The AHR/HIFα heterodimer can bind to the promoter containing three hypoxia response elements that respond to the hypoxia sensor hypoxia-inducible factor 1 [128]. Because the presence of CYP2S1 in tumors was associated with poor prognosis [129, 130] it could be used as a marker for hypoxic tumor diagnosis.

NRF2 NF-E2-related factor 2 (NRF2) is a member of the Cap'n'Collar family of basic region-leucine zipper (bZIP) transcription factors and is related to the erythroid transcription factor NF-E2 [157]. Multiple chemical inducers have been shown to activate through this element, e.g., butylated hydroxytoluene (BHT), oltipraz, sulforaphane, isothiocyanates (abundant in cruciferous vegetables), metal salts, and Michael reaction acceptors [131, 132].

Beyond the classical response of catalyzing the detoxification of carcinogens and other xenobiotics through conjugation and trapping processes, the NRF2 protein is also involved in chemoresistance by increasing glutation levels in cancer cells. In particular, induction of NRF2 causes the overexpression of glutathione *S*-transferases (GSTs), the enzymes that catalyze the conjugation of reduced glutathione to electrophilic compounds [133], as well as efflux pumps may reduce the reactivity of various anticancer drugs [134].

NRF2 is localized in the cytosol and binds to protein KEAP-1 (Kelch-like ECH-associated protein 1). Exposure to a number of stressors and inducing agents leads to dissociation of one or both of the NRF2-interacting motifs from KEAP-1, thereby rescuing NRF2 from proteasomal degradation and allowing for import into the nucleus. Once inside the nucleus, NRF2 dimerizes with small MAF proteins leading to the transactivation of several hundred cytoprotective genes, each of which contains one or more antioxidant response elements (AREs) in their promoters. Interactions with additional proteins serve to either amplify or attenuate the transcriptional response [135, 136]. The NRF2/MAF complex regulates P450s such as CYP1A1 or CYP2A5 [137].

NRF2 and AHR It is well recognized that both AHR and NRF2 signaling regulates the expression of genes affecting the metabolism of xenobiotics, and both of them are involved in cancer formation. Miao and coworkers demonstrated that NRF2 gene transcription is directly modulated by AHR activation, where the receptor directly binds to the NRF2 promoter. Moreover, silencing of AHR expression with siRNA obviated induction of NRF2 mRNA by TCDD [138]. In this way, a comprehensive set of responses to xenobiotic challenges by AHR and NRF2 can be mounted. A functional collaboration between the AHR and NRF2 pathways can also be important in cancer. Talalay and colleagues defined two types of activators of NRF2 signaling: monofunctional and bifunctional [139]. Monofunctional inducers only affect NRF2 signaling. Bifunctional inducers such as ßnaphthoflavone may interact with the AHR directly to activate AHR-regulated genes, such as CYP1A1, CYP1A2, and CYP1B1, and then undergo transformation by these enzymes to reactive intermediates that then trigger NRF2 signaling [140, 141]. The discovery of functional cooperation between AHR and NRF2 has significant biological implications. Historically, the AHR has been associated with carcinogenesis, whereas NRF2 is associated with cytoprotection against degenerative diseases. The future challenge is to determine whether crosstalk between these two transcription factors can be exploited to therapeutic advantage or to improve chemopreventive strategies [142].

NRF2 and c-jun The interplay between members of the activator protein-1 (AP-1) complex of leucine zipper

(bZIP) transcription factors, such as c-jun/c-jun, and c-fos/c-jun, has been found to regulate basal CYP2J2 expression in human liver-derived cells [143, 144]. Recent findings of Lee and coworkers now establish that heterodimers formed between NRF2 and c-Jun upregulate P450s, such as CYP2J2. In their experiments, −105/−88-base pair region of the CYP2J2 *g*ene 5′-flank as an atypical bZIP binding sequence was responsive to c-Jun/NRF2 dimers. Since CYP2J2 is the only activator of the non-sedating H1 antihistamine, ebastine, and it is also involved in the oxidation of epoxyeicosatrienoic acid (EET), discovering CYP2J2 regulation will enable the therapeutic exploitation of some of the beneficial actions of EET isomers in human tissues. EETs regulate numerous homeostatic processes, including cytoprotective and proliferative responses against injurious stresses [145] and it is also known that CYP epoxygenase 2J2 plays a role in promotion of the neoplastic cellular phenotype and in the pathogenesis of a variety of human cancers. Recognition of regulatory effect of NRF2 and c-jun on CYP2J2 in carcinoma cells could be important in potential antitumor therapy [146].

Post-transcriptional regulation

Although there are other post-transcriptional mechanisms than regulation by miRNA (alternative splicing, nuclear degradation, processing, nuclear export), not much is known about their role in carcinogenesis and we will not discuss them in this review.

miRNA regulation

miRNAs are a large family of endogenous, small regulatory RNAs that are generated by a two-step process from long primary miRNAs (pri-miRNAs) [147]. They are processed by a complex comprised of the RNase III enzyme DROSHA and an RNA-binding domain possessing protein DGCR8 (DiGeorge syndrome critical region gene 8) to 60–70 nt precursor miRNA (pre-miRNA) intermediates. Subsequently, these hairpin-shaped pre-miRNAs are transported to the cytoplasm, where they are cleaved by DICER to generate 20- to 22-nucleotide duplexes bearing two nucleotide single-stranded 3′ extensions [148]. miRNAs control the expression of a gene by targeting the 3 ‘UTR of mRNAs as a miRNA/RISC complex (RISC-RNA Induced Silencing Complex), which result ultimately in the degradation of the mRNA [149]. Human cancers commonly exhibit an altered expression profile of miRNAs with oncogenic (miR-21, miR-106a, and miR-155) or tumor-suppressive (let-7, miR-15a/16, miR-34a, and miR-143/145) activity. P450s are also regulated by miRNAs; the miRNA/RISC complex directly represses P450 protein translation, by binding to sequences in the 3′ untranslated region of P450 mRNAs or indirectly, by binding of the MRE sequences in xenosensor mRNA (Fig. 1).

Post-transcriptional regulation by miRNA could be responsible for a portion of the significant amount of unexplained interindividual variability in P450 enzyme expression and activity. Since xenobiotic-converting P450s play a role in carcinogenesis, P450-related cancer phenotypes can be modified by targeting expression of miRNAs.

Here we summarize the recent knowledge of those miRNAs that could have importance in P450s regulation during carcinogenesis.

CYP1 family Human CYP1B1, which is highly expressed in estrogen target tissues, catalyzes the metabolic activation of various procarcinogens and the 4-hydroxylation of 17-beta-estradiol. Tsuchiya and coworkers found an abundant amount of CYP1B1 protein in cancerous tissue and they identified a near-perfect matching sequence with miR-27b in the 3′-untranslated region of human *CYP1B1* (Table 4). Human *CYP1B1* is post-transcriptionally regulated by miR-27b [150]. Another brain-specific miRNA, miR-124, also downregulates *CYP1B1* directly and modulate all AHR target genes by binding to both AHR and AHRR, but its cancer relations have not yet been investigated [151].

CYP2A NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), another potent precarcinogen that can be found in tobacco products and smoke, is metabolized by CYP1A2, CYP2A6, and CYP3A4 in the liver and with CYP2A13 in the lung. NNK metabolites then form alkylating adducts with DNA, leading to genetic mutations. NNK induces tumors in multiple organs. The analogue rat enzyme for CYP2A13 is CYP2A3. Treating rats chronically with NNK, miR-34b, miR-101, miR-126, and miR-199 had lowered expression levels very early in the lungs of male F344 rats. Lowered miR-126 contributes to the increased production of CYP2A3, further activating NNK in a positive feedback loop and increasing the growth of the tumor [152].

CYP2E1 Mohri and coworkers recently found that miR-378 is involved in the post-transcriptional regulation of *CYP2E1*. The overexpression of miR-378 significantly decreased CYP2E1 protein levels and enzyme activity in the cells expressing *CYP2E1*, including 3′-UTR, but not in the cells expressing *CYP2E1* without 3′-UTR, indicating that the 3′-UTR plays a role in the miR-378-dependent repression [153]. Chronically induced *CYP2E1* with ethanol or other *CYP2E1* inducers is a high-risk factor for esophageal and gastrointestinal cancers, which gives importance to investigate transcriptional and post-transcriptional *CYP2E1* regulatory mechanisms, as basic targets in anticancer therapy.

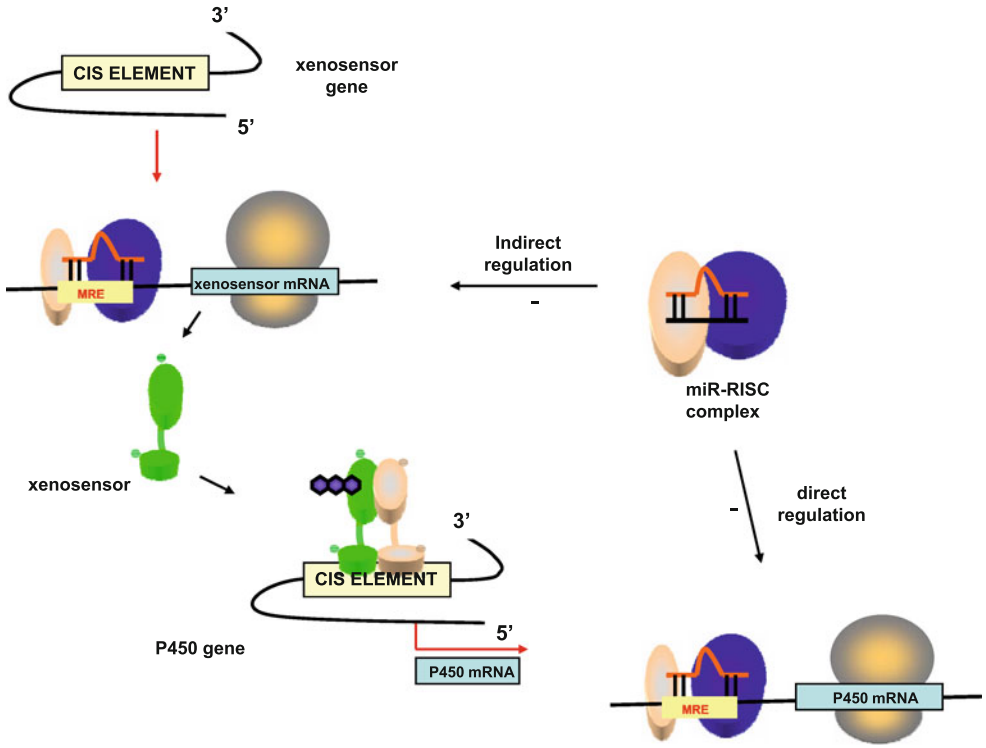

Fig. 1 Direct and indirect regulation of P450 expression by miRNA. In the cytoplasm, mature miRNA associates with a protein complex called RNA Induced Silencing Complex (RISC). The miRNA/RISC complex represses P450 protein translation directly by binding to sequences in the 3′ untranslated region of P450 mRNAs or indirectly by binding of the MRE sequences in xenosensor mRNA

Table 4 Regulation of P450s and XARs by validated miRNA molecules

miRNA	P450	miRNA response element (5′-MRE-3′)	Tissue/cell line	References
hsa-miR-27b	*CYP1B1*	3′UTR (+4358 to +4381) CAGAACUUAGCCUUUACCUGUGAA	Breast cancer	[150]
	CYP3A4	3′UTR (+612 to +589) GGUGAAAGUUAAUCCACUGUGAC	HEK 293	[155]
	VDR	3′UTR (+1754 to +1782) UUUAUGGGGGGAGAACUUACAUUGUGAA	HEK 293	[155]
hsa-miR-148a	*PXR*	3′UTR (+3359 to +3386) GCCACAGACUCUUACGUGGAGAGUGCACUGACCU	HepG2, Caco-2d LS180	[156]
hsa-miR-378	*CYP2E1*	3′UTR (+1559 to +1580) UCAAAUUGUUUGAGGUCAGGAU	HEK293	[153]

CYP3A4 Epigenetic mechanisms provide new insight into the unsolved mechanism of the large interindividual variability of CYP3A4 expressions. Since CYP3A4 is involved in the metabolism of many anticancer drugs, from which many have a low therapeutic window (e.g., doxorubicine, ifosfamide, erlotinib), determining its metabolic capacity is very important. Lamba et al. reported that variability in hepatic CYP3A4 cannot be explained just by common *CYP3A4* coding variants [154], suggesting the role of other mechanisms, such as regulation with miRNAs or inherited modifications in the miRNA gene itself. Until now, one miRNA, miR-27b, has been described to regulate *CYP3A4* expression directly binding to the miRNA response element (MRE) within the 3'UTR region of *CYP3A4* mRNA [155].

Some miRNAs, such as miR-148a, which is selectively and abundantly expressed in the liver, regulates other liver specific genes, for e.g., the human PXR receptor. miR-148a binds to the 3′-UTR region of PXR mRNA, thereby decreasing synthesis of PXR protein. Since CYP3A4 is a target for PXR, miR-148a indirectly modulates the inducible and/or constitutive levels of *CYP3A4* expression [156]. Another example of indirect modulation would be the VDR receptor. VDR also regulates CYP3A4 (see cross talk VDR/PXR or VDR/CAR) and VDR could be down-regulated with miR-27b [153].

Conclusions

In this review, various examples of P450 regulation mechanisms were presented, which all contribute to the amount of finally translated P450 mRNA.

The P450s responsible for the activation or inactivation of precarcinogens and anticancer drugs are polymorphic. Considerable research has been directed to elucidate to what extent genetic polymorphism in the corresponding genes could affect susceptibility for environmentally induced cancer and for cancer therapy (for e.g., in a recent study, sex and polymorphisms in *FoxA2*, *HNF4α*, *FoxA3*, *PXR*, ABCB1, and the *CYP3A4* promoter together explained 24.6% of the variation in hepatic *CYP3A4* expression). The remaining 75.4% of variations depends on individual regulatory patterns (transcriptional, post-transcriptional or post-translational regulation) of *CYP3A4* expression.

Understanding the molecular regulation of P450s with these receptors and enzymes, deducing new endogenous ligands for the nuclear receptors, and identification of novel miRNAs will be the next challenges to establish new markers of carcinogenesis and new therapeutical, cancer-related concepts.

References

1. Waxman DJ, Azaroff L (1992) Phenobarbital induction of P-450 gene expression. Biochem J 281:577–592
2. Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, Waterman MR, Gotoh O, Coon MJ, Estabrook RW (1996) P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 6:1–42
3. Rodriguez-Antona C, Ingelman-Sundberg M (2006) Cytochrome P450 pharmacogenetics and cancer. Oncogene 25(11):1679–1691
4. McFadyen MC, Cruickshank ME, Miller ID, McLeod HL, Melvin WT, Haites NE, Parkin D, Murray GI (2001) Cytochrome P450 CYP1B1 over-expression in primary and metastatic ovarian cancer. Br J Cancer85(2):242–246
5. McFadyen MC, McLeod HL, Jackson FC, Melvin WT, Doehmer J, Murray GI (2001) Cytochrome P450 CYP1B1 protein expression: a novel mechanism of anticancer drug resistance. Biochem Pharmacol 62(2):207–212
6. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C (2007) Influence of polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther 116(3):496–526
7. Rodriguez-Antona C, Gomez A, Karlgren M, Sim SC, Ingelman-Sundberg M (2010) Molecular genetics and epigenetics of the cytochrome P450 gene family and its relevance for cancer risk and treatment. Hum Genet 127(1):1–17
8. Handschin C, Meyer UA (2003) Induction of drug metabolism: the role of nuclear receptors. Pharmacol Rev 55(4):649–673
9. Pascussi JM, Gerbal-Chaloin S, Duret C, Daujat-Chavanieu M, Vilarem MJ, Maurel P (2008) The tangle of nuclear receptors that controls xenobiotic metabolism and transport: crosstalk and consequences. Annu Rev Pharmacol Toxicol 48:1–32
10. Lim YP, Huang JD (2008) Interplay of pregnane X receptor with other nuclear receptors on gene regulation. Drug Metab Pharmacokinet 23(1):14–21
11. Takai D, Jones PA (2003) The CpG island searcher: a new WWW resource. In Silico Biol 3(3):235–240
12. Tate PH, Bird AP (1993) Effects of DNA methylation on DNA-binding proteins and gene expression. Curr Opin Genet Dev 3:226–231
13. Rountree MR, Bachman KE, Herman JG, Baylin SB (2001) DNA methylation, chromatin inheritance and cancer. Oncogene 20:3156–3165
14. Weber M, Hellmann I, Stadler MB, Ramos L, Paabo S, Rebhan M, Schubeler D (2007) Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. Nat Genet 39:457–466
15. De Smet C, Lurquin C, Lethe B, Martelange V, Boon T (1999) DNA methylation is the primary silencing mechanism for a set of germ line- and tumor-specific genes with a CpG-rich promoter. Mol Cell Biol 19(11):7327–7335
16. Stein R, Razin A, Cedar H (1982) In vitro methylation of the hamster adenine phosphoribosyltransferase gene inhibits its expression in mouse L cells. Proc Natl Acad Sci USA 79:3418–3422
17. Futscher BW, Oshiro MM, Wozniak RJ, Holtan N, Hanigan CL, Duan H, Domann FE (2002) Role for DNA methylation in the control of cell type specific maspin expression. Nat Genet 31:175–179
18. Song F, Smith JF, Kimura MT, Morrow AD, Matsuyama T, Nagase H, Held WA (2005) Association of tissue-specific differentially methylated regions (TDMs) with differential gene expression. Proc Natl Acad Sci USA 102:3336–3341
19. Okino ST, Pookot D, Li LC, Zhao H, Urakami S, Shiina H, Dahiya R (2006) Epigenetic inactivation of the dioxin-responsive cytochrome P4501A1 gene in human prostate cancer. Cancer Res 66:7420–7428
20. Anttila S, Hakkola J, Tuominen P, Elovaara E, Husgafvel-Pursiainen K, Karjalainen A, Hirvonen A, Nurminen T (2003) Methylation of cytochrome P4501A1 promoter in the lung is associated with tobacco smoking. Cancer Res 63:8623–8628
21. Kellermann G, Shaw CR, Luyten-Kellermann M (1973) Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. N Engl J Med 289:934–937
22. Stücker I, Jacquet M, de Waziers I, Cénée S, Beaune P, Kremers P, Hémon D (2000) Relation between inducibility of CYP1A1, GSTM1 and lung cancer in a French population. Pharmacogenetics 10:617–627
23. Murray GI, Taylor MC, McFadyen MCMcKay JA, Greenlee WF, Burke MD, Melvin WT (1997) Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res 57:3026–3031
24. McFadyen MC, Breeman S, Payne S, Stirk C, Miller ID, Melvin WT, Murray GI (1999) Immunohistochemical localization of cytochrome P450 CYP1B1 in breast cancer with monoclonal antibodies specific for CYP1B1. J Histochem Cytochem 47:1457–1464
25. Tokizane T, Shiina H, Igawa M, Enokida H, Urakami S, Kawakami T, Ogishima T, Okino ST, Li LC, Tanaka Y, Nonomura N, Okuyama A, Dahiya R (2005) Cytochrome P450 1B1 is overexpressed and regulated by hypomethylation in prostate cancer. Clin Cancer Res 11:5793–5801
26. Habano W, Gamo T, Sugai T, Otsuka K, Wakabayashi G, Ozawa S (2009) CYP1B1, but not CYP1A1, is downregulated by promoter methylation in colorectal cancers. Int J Oncol 34(4):1085–1091
27. Vieira I, Pasanen M, Raunio H, Cresteil T (1998) Expression of CYP2E1 in human lung and kidney during development and in

full-term placenta: a differential methylation of the gene is involved in the regulation process. Pharmacol Toxicol 83(5):183–187
28. Vieira I, Sonnier M, Cresteil T (1996) Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476–483
29. Botto F, Seree E, el Khyari S, de Sousa G, Massacrier A, Placidi M, Cau P, Pellet W, Rahmani R, Barra Y (1994) Tissue-specific expression and methylation of the human CYP2E1 gene. Biochem Pharmacol 48(6):1095–1103
30. Ghanayem BI, Hoffler U (2007) Investigation of xenobiotics metabolism, genotoxicity and carcinogenicity using cyp2e1 (−/−) mice. Curr Drug Metab 8:728–749
31. Botto F, Seree E, el Khyari S, Cau P, Henric A, De Meo M, Bergeron P, Barra Y (1994) Hypomethylation and hypoexpression of human CYP2E1 gene in lung tumors. Biochem Biophys Res Commun 205(2):1086–1092
32. Li W, Tang Y, Hoshino T, Neya S (2009) Molecular modeling of human cytochrome P450 2W1 and its interactions with substrates. Mol Graph Model 28(2):170–176
33. Gomez A, Nekvindova J, Travica S, Lee MY, Johansson I, Edler D, Mkrtchian S, Ingelman-Sundberg M (2010) Colorectal cancer specific cytochrome P450 2W1 (CYP2W1): intracellular localization, glycosylation, and catalytic activity. Mol Pharmacol. doi: 10.1124/mol.110.067652
34. Edler D, Stenstedt K, Ohrling K, Hallstrom M, Karlgren M, Ingelman-Sundberg M, Ragnhammar P (2009) The expression of the novel CYP2W1 enzyme is an independent prognostic factor in colorectal cancer—a pilot study. Eur J Cancer 45(4):705–712
35. Karlgren M, Gomez A, Stark K, Svärd J, Rodriguez-Antona C, Oliw E, Bernal ML, Ramón y Cajal S, Johansson I, Ingelman-Sundberg M (2006) Tumor-specific expression of the novel cytochrome P450 enzyme, CYP2W1. Biochem Biophys Res Commun 341(2):451–458
36. Karlgren M, Ingelman-Sundberg M (2007) Tumour-specific expression of CYP2W1: its potential as a drug target in cancer therapy. Expert Opin Ther Targets 11(1):61–67
37. Gomez A, Karlgren M, Edler D, Bernal ML, Mkrtchian S, Ingelman-Sundberg M (2007) Expression of CYP2W1 in colon tumors: regulation by gene methylation. Pharmacogenomics 8(10):1315–1325
38. Dannenberg LO, Edenberg HJ (2006) Epigenetics of gene expression in human hepatoma cells: expression profiling the response to inhibition of DNA methylation and histone deacetylation. BMC Genomics 7:181
39. Kouzarides T (2007) Chromatin modifications and their function. Cell 128:693–705
40. Jenuwein T, Allis CD (2001) Translating the histone code. Science 293:1074–1080
41. Yoon HG, Chan DW, Reynolds AB, Qin J, Wong J (2003) N-CoR mediates DNA methylation-dependent repression through a methyl CpG binding protein. Kaiso Mol Cell 12:723–734
42. Chi P, Allis CD, Wang GG (2010) Covalent histone modifications–miswritten, misinterpreted and mis-erased in human cancers. Nat Rev Cancer 10(7):457–469
43. Schnekenburger M, Peng L, Puga A (2007) HDAC1 bound to the Cyp1a1 promoter blocks histone acetylation associated with Ah receptor-mediated trans-activation. Biochim Biophys Acta 1769(9–10):569–578
44. Xie Y, Ke S, Ouyang N, He J, Xie W, Bedford MT, Tian Y (2009) Epigenetic regulation of transcriptional activity of pregnane X receptor by protein arginine methyltransferase 1. J Biol Chem 284(14):9199–9205
45. Assenat E, Gerbal-Chaloin S, Larrey D, Saric J, Fabre JM, Maurel P, Vilarem MJ, Pascussi JM (2004) Interleukin 1beta inhibits CAR-induced expression of hepatic genes involved in drug and bilirubin clearance. Hepatology 40(4):951–960
46. Ma Quiang (2008) Xenobiotic-activated receptors: from transcription to drug metabolism to disease. Chem Res Toxicol 21(9):1651–1671
47. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM (1995) The nuclear receptor superfamily: the second decade. Cell 83(6):835–839
48. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ (2006) Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. Cell 126(4):789–799
49. Tamási V, Vereczkey L, Falus A, Monostory K (2003) Some aspects of interindividual variations in the metabolism of xenobiotics. Inflamm Res 52(8):322–333
50. Moore LB, Maglich JM, McKee DD, Wisely B, Willson TM, Kliewer SA, Lambert MH, Moore JT (2002) Pregnane X receptor (PXR), constitutive androstane receptor (CAR), and benzoate X receptor (BXR) define three pharmacologically distinct classes of nuclear receptors. Mol Endocrinol 16(5):977–986
51. Goodwin B, Hodgson E, Liddle C (1999) The orphan human Pregnane X Receptor mediates the transcriptional activation of CYP3A4 by rifampicin through a distal enhancer module. Mol Pharmacol 56:1329–1339
52. Sueyoshi T, Negishi M (2001) Phenobarbital response elements of cytochrome P450 genes and nuclear receptors. Annu Rev Pharmacol Toxicol 41:123–143
53. Gerbal-Chaloin S, Pascussi JM, Pichard-Garcia L, Daujat M, Waechter F, Fabre JM, Carrere N, Maurel P (2001) Induction of CYP2C genes in human hepatocytes in primary culture. Drug Metab Dispos 29:242–251
54. Leo C, Chen JD (2000) The SRC family of nuclear receptor coactivators. Gene 245:1–11
55. Hörlein AJ, Näär AM, Heinzel T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Söderström M, Glass CK (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature 377:397–404
56. Chen JD, Evans RM (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 377:454–457
57. Ordentlich P, Downes M, Xie W, Genin A, Spinner NB, Evans RM (1999) Unique forms of human and mouse nuclear receptor corepressor SMRT. Proc Natl Acad Sci USA 96:2639–2644
58. Park EJ, Schroen DJ, Yang M, Li H, Li L, Chen JD (1999) SMRT, a silencing mediator for retinoid and thyroid hormone receptors-extended isoform that is more related to the nuclear receptor corepressor. Proc Natl Acad Sci USA 96:3519–3524
59. Chang TK, Weber GF, Crespi CL, Waxman DJ (1993) Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes. Cancer Res 53:5629–5637
60. Chang TK, Yu L, Maurel P, Waxman DJ (1997) Enhanced cyclophosphamide and ifosfamide activation in primary human hepatocyte cultures: response to cytochrome P-450 inducers and autoinduction by oxazaphosphorines. Cancer Res 57:1946–1954
61. Crewe HK, Ellis SW, Lennard MS, Tucker GT (1997) Variable contribution of cytochromes P450 2D6, 2C9 and 3A4 to the 4-hydroxylation of tamoxifen by human liver microsomes. Biochem Pharmacol 53:171–178
62. Desai PB, Nallani SC, Sane RS, Moore LB, Goodwin BJ, Buckley DJ, Buckley AR (2002) Induction of cytochrome P450 3A4 in primary human hepatocytes and activation of the human

pregnane X receptor by tamoxifen and 4-hydroxytamoxifen. Drug Metab Dispos 30:608–612
63. Mani S, Huang H, Sundarababu S, Liu W, Kalpana G, Smith AB, Horwitz SB (2005) Activation of the steroid and xenobiotic receptor (human pregnane X receptor) by nontaxane microtubule stabilizing agents. Clin Cancer Res 11:6359–6369
64. Synold TW, Dussault I, Forman BM (2001) The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. Nat Med 7:584–590
65. Wang H, Faucette S, Sueyoshi T, Moore R, Ferguson S, Negishi M, LeCluyse EL (2003) A novel distal enhancer module regulated by pregnane X receptor/constitutive androstane receptor is essential for the maximal induction of CYP2B6 gene expression. J Biol Chem 278:14146–14152
66. Sueyoshi T, Negishi M (2001) Phenobarbital response elements of cytochrome P450 genes and nuclear receptors. Annu Rev Pharmacol Toxicol 41:123–143
67. Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliewer S, Willson TM, Edwards PA (2002) Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. J Biol Chem 277:2908–2915
68. Faucette SR, Sueyoshi T, Smith CM, Negishi M, Lecluyse EL, Wang H (2006) Differential regulation of hepatic CYP2B6 and CYP3A4 genes by constitutive androstane receptor but not pregnane X receptor. J Pharmacol Exp 317(3):1200–1209
69. Njar VC, Gediya L, Purushottamachar P, Chopra P, Vasaitis TS, Khandelwal A, Mehta J, Huynh C, Belosay A, Patel J (2006) Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases. Bioorg Med Chem 14(13):4323–4340
70. Kato S (2000) The function of vitamin D activation. J Biochem 127:717–722
71. Wang K, Mendy AJ, Dai G, Luo HR, He L, Wan YJ (2006) Retinoids activate the RXR/SXR-mediated pathway and induce the endogenous CYP3A4 activity in Huh7 human hepatoma cells. Toxicol Sci 92:51–60
72. Thummel KE, Brimer C, Yasuda K, Thottassery J, Senn T, Lin Y, Ishizuka H, Kharasch E, Schuetz J, Schuetz E (2001) Transcriptional control of intestinal cytochrome P-4503A by 1alpha, 25-dihydroxy vitamin D3. Mol Pharmacol 60:1399–1406
73. Drocourt L, Ourlin JC, Pascussi JM, Maurel P, Vilarem MJ (2002) Expression of CYP3A4, CYP2B6, and CYP2C9 is regulated by the vitamin D receptor pathway in primary human hepatocytes. J Biol Chem 277:25125–25132
74. Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, Mangelsdorf DJ (2002) Vitamin D receptor as an intestinal bile acid sensor. Science 296:1313–1316
75. Guyton KZ, Kensler TW, Posner GH (2001) Cancer chemoprevention using natural vitamin D and synthetic analogs. Annu Rev Pharmacol Toxicol 41:421–442
76. Pascussi JM, Drocourt L, Fabre JM, Maurel P, Vilarem MJ (2000) Dexamethasone induces pregnane X receptor and retinoid X receptor-alpha expression in human hepatocytes: synergistic increase of CYP3A4 induction by pregnane X receptor activators. Mol Pharmacol 58:361–372
77. Wang H, Faucette SR, Gilbert D, Jolley SL, Sueyoshi T, Negishi M, LeCluyse EL (2003) Glucocorticoid receptor enhancement of pregnane X receptor-mediated CYP2B6 regulation in primary human hepatocytes. Drug Metab Dispos 31:620–630
78. Loose DS, Stover EP, Feldman D (1983) Ketoconazole binds to glucocorticoid receptors and exhibits glucocorticoid antagonist activity in cultured cells. J Clin Invest 72:404–408
79. Chen Y, Kissling G, Negishi M, Goldstein JA (2005) The nuclear receptors constitutive androstane receptor and pregnane X receptor cross talk with hepatic nuclear factor 4alpha to synergistically activate the human CYP2C9 promoter. J Pharmacol Exp Ther 314:1125–1133
80. Liu FJ, Song X, Yang D, Deng R, Yan B (2008) The far and distal enhancers in the CYP3A4 gene coordinate the proximal promoter in responding similarly to the pregnane X receptor but differentially to hepatocyte nuclear factor-4alpha. Biochem J 409:243–250
81. Kawana K, Ikuta T, Kobayashi Y, Gotoh O, Takeda K, Kawajiri K (2003) Molecular mechanism of nuclear translocation of an orphan nuclear receptor, SXR. Mol Pharmacol 63(3):524–531
82. Zelko I, Sueyoshi T, Kawamoto T, Moore R, Negishi M (2001) The peptide near the C terminus regulates receptor CAR nuclear translocation induced by xenochemicals in mouse liver. Mol Cell Biol 21(8):2838–2846
83. Rencurel F, Foretz M, Kaufmann MR, Stroka D, Looser R, Leclerc I, da Silva Xavier G, Rutter GA, Viollet B, Meyer UA (2006) Stimulation of AMP-activated protein kinase is essential for the induction of drug metabolizing enzymes by phenobarbital in human and mouse liver. Mol Pharmacol 70(6):1925–1934
84. Blättler SM, Rencurel F, Kaufmann MR, Meyer UA (2007) In the regulation of cytochrome P450 genes, phenobarbital targets LKB1 for necessary activation of AMP-activated protein kinase. Proc Natl Acad Sci USA 104(3):1045–1050
85. Choi E, Lee S, Yeom SY, Kim GH, Lee JW, Kim SW (2005) Characterization of activating signal cointegrator-2 as a novel transcriptional coactivator of the xenobiotic nuclear receptor constitutive androstane receptor. Mol Endocrinol 19:1711–1719
86. Kim HJ, Lee SK, Na SY, Choi HS, Lee JW (1998) Molecular cloning of xSRC-3, a novel transcription coactivator from Xenopus, that is related to AIB1, p/CIP, and TIF2. Mol Endocrinol 12:1038–1047
87. Min G, Kemper JK, Kemper B (2002) Glucocorticoid receptor-interacting protein 1 mediates ligand-independent nuclear translocation and activation of constitutive androstane receptor in vivo. J Biol Chem 277:26356–26363
88. Muangmoonchai R, Smirlis D, Wong SC, Edwards M, Phillips IR, Shephard EA (2001) Xenobiotic induction of cytochrome P450 2B1 (CYP2B1) is mediated by the orphan nuclear receptor constitutive androstane receptor (CAR) and requires steroid co-activator 1 (SRC-1) and the transcription factor Sp1. Biochem J 355:71–78
89. Shiraki T, Sakai N, Kanaya E, Jingami H (2003) Activation of orphan nuclear constitutive androstane receptor requires subnuclear targeting by peroxisome proliferator-activated receptor γ coactivator-1α. A possible link between xenobiotic response and nutritional state. J Biol Chem 278:11344–11350
90. Inoue K, Borchers CH, Negishi M (2006) Cohesin protein SMC1 represses the nuclear receptor CAR-mediated synergistic activation of a human P450 gene by xenobiotics. Biochem J 398:125–133
91. Schmidt R, Baumann F, Knupfer H, Brauckhoff M, Horn LC, Schonfelder M, Kohler U, Preiss R (2004) CYP3A4, CYP2C9 and CYP2B6 expression and ifosfamide turnover in breast cancer tissue microsomes. Br J Cancer 90(4):911–916
92. El-Rayes BF, Ali S, Heilbrun LK, Lababidi S, Bouwman D, Visscher D, Philip PA (2003) Cytochrome p450 and glutathione transferase expression in human breast cancer. Clin Cancer Res 9(5):1705–1709
93. Williams JA, Phillips DH (2000) Mammary expression of xenobiotic metabolizing enzymes and their potential role in breast cancer. Cancer Res 60(17):4667–4677
94. de Jonge ME, Huitema AD, van Dam SM, Beijnen JH, Rodenhuis S (2005) Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin. Cancer Chemother Pharmacol 55(5):507–510

95. Harmsen S, Meijerman I, Beijnen JH, Schellens JH (2007) The role of nuclear receptors in pharmacokinetic drug-drug interactions in oncology. Cancer Treat Rev 33(4):369–380
96. Tsunedomi R, Iizuka N, Hamamoto Y, Uchimura S, Miyamoto T, Tamesa T, Okada T, Takemoto N, Takashima M, Sakamoto K, Hamada K, Yamada-Okabe H, Oka M (2005) Patterns of expression of cytochrome P450 genes in progression of hepatitis C virus associated hepatocellular carcinoma. Int J Oncol 27(3):661–667
97. Puigserver PJ, Rhee J, Donovan CJ, Walkey J, Cliff Yoon F, Oriente Y, Kitamura J, Altomonte H, Dong D, Accili B, Spiegelman M (2003) Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1α interaction. Nature 423:550–555
98. Accili D, Arden KC (2004) FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. Cell 117(4):421–426
99. Kodama S, Koike C, Negishi M, Yamamoto Y (2004) Nuclear receptors CAR and PXR cross talk with FOXO1 to regulate genes that encode drug-metabolizing and gluconeogenic enzymes. Mol Cell Biol 2(18):7931–7940
100. Wolf I, Rubinek T (2008) Diabetes mellitus and breast cancer. Front Diabetes 19:97–113
101. Pascussi J, Busson-Le Coniat M, Maurel P, Vilarem M (2003) Transcriptional analysis of the orphan nuclear receptor constitutive androstane receptor (NR1I3) gene promoter: identification of a distal glucocorticoid responsive element. Mol Endocrinol 17:42–55
102. Wang H, Faucette SR, Gilbert D, Jolley SL, Sueyoshi T, Negishi M, LeCluyse EL (2003) Glucocorticoid receptor enhancement of pregnane X receptor-mediated CYP2B6 regulation in primary human hepatocytes. Drug Metab Dispos 31(5):620–630
103. Chen Y, Goldstein JA (2009) The transcriptional regulation of the human CYP2C genes. Curr Drug Metab 10(6):567–578
104. Hankinson O (1995) The aryl hydrocarbon receptor complex. Ann Rev Pharmacol Toxicol 35:307–340
105. Androutsopoulos VP, Tsatsakis AM, Spandidos DA (2009) Cytochrome P450 CYP1A1: wider roles in cancer progression and prevention. BMC Cancer 16(9):187
106. Dietrich C, Kaina B (2010) The aryl hydrocarbon receptor (AhR) in the regulation of cell-cell contact and tumor growth. Carcinogenesis 31(8):1319–1328
107. Puga A, Ma C, Marlowe JL (2009) The aryl hydrocarbon receptor cross-talks with multiple signal transduction pathways. Biochem Pharmacol 77:713–722
108. Mimura J, Ema M, Sogawa K, Fujii-Kuriyama Y (1999) Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. Genes Dev 13(1):20–25
109. Hankinson O (2005) Role of coactivators in transcriptional activation by the aryl hydrocarbon receptor. Arch Biochem Biophys 433:379–386
110. Ma Q (2007) Aryl hydrocarbon receptor degradation-promoting factor (ADPF) and the control of the xenobiotic response. Mol Interv 7(3):133–137
111. Wang SH, Liang CT, Liu YW, Huang MC, Huang SC, Hong WF, Su JG (2009) Crosstalk between activated forms of the aryl hydrocarbon receptor and glucocorticoid receptor. Toxicology 262(2):87–97
112. Monostory K, Kohalmy K, Prough RA, Kóbori L, Vereczkey L (2005) The effect of synthetic glucocorticoid, dexamethasone on CYP1A1 inducibility in adult rat and human hepatocytes. FEBS Lett 579(1):229–235
113. Dvoøak Z, Vrzal R, Pávek P, Ulrichová J (2008) An evidence for regulatory cross-talk between aryl hydrocarbon receptor and glucocorticoid receptor in HepG2 cells. Physiol Res 57:427–435
114. Vrzal R, Stejskalova L, Monostory K, Maurel P, Bachleda P, Pavek P, Dvorak Z (2009) Dexamethasone controls aryl hydrocarbon receptor (AhR)-mediated CYP1A1 and CYP1A2 expression and activity in primary cultures of human hepatocytes. Chem Biol Interact 179:288–296
115. van Erp NP, Gelderblom H, Guchelaar HJ (2009) Clinical pharmacokinetics of tyrosine kinase inhibitors. Cancer Treat Rev 35(8):692–706
116. Pearce ST, Liu H, Radhakrishnan I, Abdelrahim M, Safe S, Jordan VC (2004) Interaction of the aryl hydrocarbon receptor ligand 6-methyl-1, 3, 8-thrichlorodibenzofuran with oestrogen receptor alpha. Cancer Res 64:2889–2897
117. Safe S, Wormke M (2003) Inhibitory aryl hydrocarbon receptor-estrogen receptor alpha cross-talk and mechanisms of action. Chem Res Toxicol 16:807–816
118. Matthews J, Wihlén B, Thomsen J, Gustafsson J (2005) Aryl hydrocarbon receptor-mediated transcription: ligand-dependent recruitment of estrogen receptor α to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-responsive promoters. Mol Cell Biol 25:5317–5328
119. Han W, Pentecost BT, Pietropaolo RL, Fasco MJ, Spivack SD (2005) Estrogen receptor α increases basal and cigarette smoke extract-induced expression of CYP1A1 and CYP1B1, but not GSTP1 in normal human bronchial epithelial cells. Mol Carcinogen 44:202–211
120. Ohtake F, Takeyama K, Matsumoto H, Kitagawa H, Yamamoto Y, Nohara K, Tohyama C, Krust A, Mimura J, Chambon P, Yanagisawa J, Fujii-Kuriyama Y, Kato S (2003) Modulation of oestrogen receptor signaling by association with the activated dioxin receptor. Nature 423:545–550
121. Shibata H, Spencer TE, Onate SA, Jenster G, Tsai SY, Tsai MJ, O'Malley BW (1997) Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action. Recent Prog Horm Res 52:141–164
122. Monostory K, Pascussi JM, Kóbori L, Dvorak Z (2009) Hormonal regulation of CYP1A expression. Drug Metab Rev 41(4):547–572
123. Ema M, Hirota K, Mimura J, Abe H, Yodoi J, Sogawa K, Poellinger L, Fujii-Kuriyama Y (1999) Molecular mechanisms of transcription activation by HLF and HIF1alpha in response to hypoxia: their stabilization and redox signal-induced interaction with CBP/p300. EMBO J 18:1905–1914
124. Fritz WA, Lin TM, Peterson RE (2008) The aryl hydrocarbon receptor (AhR) inhibits vanadate-induced vascular endothelial growth factor (VEGF) production in TRAMP prostates. Carcinogenesis 29(5):1077–1082
125. Nishida CR, Lee M, de Montellano PR (2010) Efficient hypoxic activation of the anticancer agent AQ4N by CYP2S1 and CYP2W1. Mol Pharmacol 78(3):497–502
126. Karlgren M, Miura S, Ingelman-Sundberg M (2005) Novel extrahepatic cytochrome P450s. Toxicol Appl Pharmacol 207:57–61
127. Rylander T, Neve EP, Ingelman-Sundberg M, Oscarson M (2001) Identification and tissue distribution of the novel human cytochrome P450 2S1 (CYP2S1). Biochem Biophys Res Commun 281:529–535
128. Rivera SP, Wang F, Saarikoski ST, Taylor RT, Chapman B, Zhang R, Hankinson O (2007) A novel promoter element containing multiple overlapping xenobiotic and hypoxia response elements mediates induction of P4502S1 by both dioxin and hypoxia. J Biol Chem 282:10881–10893
129. Downie D, McFadyen MC, Rooney PH, Cruickshank ME, Parkin DE, Miller ID, Telfer C, Melvin WT, Murray GI (2005) Profiling cytochrome P450 expression in ovarian cancer: identification of prognostic markers. Clin Cancer Res 11:7369–7375
130. Kumarakulasingham M, Rooney PH, Dundas SR, Telfer C, Melvin WT, Curran S, Murray GI (2005) Cytochrome p450 profile of colorectal cancer: identification of markers of prognosis. Clin Cancer Res 11:3758–3765

131. Shih AY, Li P, Murphy TH (2005) A small-molecule-inducible Nrf2-mediated antioxidant response provides effective prophylaxis against cerebral ischemia in vivo. J Neurosci 25(44): 10321–10335
132. Tamasi V, Jeffries JM, Arteel GE, Falkner KC (2004) Ebselen augments its peroxidase activity by inducing nrf-2-dependent transcription. Arch Biochem Biophys 431(2):161–168
133. Douglas KT (1987) Mechanism of action of glutathione-dependent enzymes. Adv Enzymol Relat Areas Mol Biol 59103–59167
134. Sau F, Pellizzari Tregno F, Valentino F, Federici G, Caccuri AM (2010) Glutathione transferases and development of new principles to overcome drug resistance. Arch Biochem Biophys 500116–122
135. Tong KI, Kobayashi A, Katsuoka F, Yamamoto M (2006) Two-site substrate recognition model for the Keap1-Nrf2 system: a hinge and latch mechanism. Biol Chem 387:1311–1320
136. Hayes JD, McMahon M (2009) NRF2 and KEAP1 mutations: permanent activation of an adaptive response in cancer. Trends Biochem Sci 34:176–188
137. Lämsä V, Levonen AL, Leinonen H, Ylä-Herttuala S, Yamamoto M, Hakkola J (2010) Cytochrome P450 2A5 constitutive expression and induction by heavy metals is dependent on redox-sensitive transcription factor Nrf2 in liver. Chem Res Toxicol 23(5):977–985
138. Miao W, Hu L, Scrivens PJ, Batist G (2005) Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: direct cross-talk between phase I and II drug-metabolizing enzymes. J Biol Chem 280:20340–20348
139. Prochaska HJ, Talalay P (1988) Regulatory mechanisms of monofunctional and bifunctional anticarcinogenic enzyme inducers in murine liver. Cancer Res 48:4776–4782
140. Kohle C, Bock KW (2007) Coordinate regulation of Phase I and II xenobiotic metabolisms by the Ah receptor and Nrf2. Biochem Pharmacol 73:1853–1862
141. Kensler TW, Wakabayashi N, Slocum SL, Skoko JJ, Shin S (2010) When Nrf2 talks, who's listening? Antioxid Redox Signal 13(11):1649–1663
142. Hayes JD, Dinkova-Kostova AT, McMahon M (2009) Cross-talk between transcription factors AhR and Nrf2: lessons for cancer chemoprevention from dioxin. Toxicol Sci 111(2):199–201
143. Marden NY, Fiala-Beer E, Xiang SH, Murray M (2003) Role of activator protein-1 in the down-regulation of the human CYP2J2 gene in hypoxia. Biochem J 373:669–680
144. Marden NY, Murray M (2005) Characterization of a c-Jun-responsive module in the 5′flank of the human CYP2J2 gene that regulates transactivation. Biochem J 391:631–640
145. Lee AC, Murray M (2010) Up-regulation of human CYP2J2 in HepG2 cells by butylated hydroxyanisole is mediated by c-Jun and Nrf2. Mol Pharmacol 77(6):987–994
146. Jiang JG, Chen CL, Card JW, Yang S, Chen JX, Fu XN, Ning YG, Xiao X, Zeldin DC, Wang DW (2005) Cytochrome P450 2J2 promotes the neoplastic phenotype of carcinoma cells and is up-regulated in human tumors. Cancer Res 65(11):4707–4715
147. Ambros V (2004) The functions of animal microRNAs. Nature 431:350–355
148. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116:281–297
149. Molnár V, Tamási V, Bakos B, Wiener Z, Falus A (2008) Changes in miRNA expression in solid tumors: an miRNA profiling in melanomas. Semin Cancer Biol 18(2):111–122
150. Tsuchiya Y, Nakajima M, Takagi S, Taniya T, Yokoi T (2006) MicroRNA regulates the expression of human cytochrome P450 1B1. Cancer Res 66(18):9090–9098
151. Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM (2005) Title microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature 433(7027):769–773
152. Kalscheuer S, Zhang X, Zeng Y, Upadhyaya P (2008) Differential expression of microRNAs in early-stage neoplastic transformation in the lungs of F344 rats chronically treated with the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Carcinogenesis 29(12):2394–2399
153. Mohri T, Nakajima M, Fukami T, Takamiya M, Aoki Y, Yokoi T (2010) Human CYP2E1 is regulated by miR-378. Biochem Pharmacol 79(7):1045–1052
154. Lamba V, Panetta JC, Strom S, Schuetz EG (2010) Genetic predictors of interindividual variability in hepatic CYP3A4 expression. J Pharmacol Exp Ther 332:1088–1099
155. Pan YZ, Gao W, Yu AM (2009) MicroRNAs regulate CYP3A4 expression via direct, indirect targeting. Drug Metab Dispos 37(10):2112–2117
156. Takagi S, Nakajima M, Mohri T, Yokoi T (2008) Post-transcriptional regulation of human pregnane X receptor by micro-RNA affects the expression of cytochrome P450 3A4. J Biol Chem 283(15):9674–9680