REVIEW ARTICLE

Regulation of cytochrome P450 (*CYP*) genes by nuclear receptors

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Members of the nuclear-receptor superfamily mediate crucial physiological functions by regulating the synthesis of their target genes. Nuclear receptors are usually activated by ligand binding. Cytochrome P450 (CYP) isoforms often catalyse both formation and degradation of these ligands. CYPs also metabolize many exogenous compounds, some of which may act as activators of nuclear receptors and disruptors of endocrine and cellular homoeostasis. This review summarizes recent findings that indicate that major classes of *CYP* genes are selectively regulated by certain ligand-activated nuclear receptors, thus creating tightly controlled networks.

Key words: endobiotic metabolism, gene expression, gene transcription, ligand-activated, xenobiotic metabolism.

INTRODUCTION

Overview of the cytochrome P450 (CYP) superfamily

CYPs constitute a superfamily of haem-thiolate proteins present in prokaryotes and throughout the eukaryotes. CYPs act as mono-oxygenases, with functions ranging from the synthesis and degradation of endogenous steroid hormones, vitamins and fatty acid derivatives ('endobiotics') to the metabolism of foreign compounds such as drugs, environmental pollutants, and carcinogens ('xenobiotics') [1]. At present, 17 mammalian *CYP* gene families collectively encode about 60 distinct CYP forms in any given species [2], a number expected to rise by the completion of genome-wide sequencing projects. On the basis of crystal structures of bacterial P450s, molecular modelling and site-directed mutagenesis, the overall structure of mammalian membrane-bound P450 has been deduced and residues required for substrate binding, electron transfer and haem binding have been identified [3,4].

CYPs in gene families 1–4 exhibit broad, but overlapping, substrate and product specificities that may vary between corresponding forms from different species [1,5]. Their ability to metabolize a wide array of xenobiotics [6], the inducibility of many CYP forms by xenobiotics [7–9] and documented gene polymorphisms [10,11] have all contributed to an explosion of literature on CYP-dependent drug metabolism. To name just a few examples, differences in the amounts and intrinsic capacities of CYP forms to metabolize a particular drug or chemical may influence profoundly drug–drug interactions, drug or carcinogen activation and detoxification, or species differences in CYP-catalysed reactions of toxic chemicals. The CYPs in families 1–4 also metabolize endogenous compounds, including steroids and bile acids, fatty acids, prostaglandins and other eicosanoids, and retinoids [6,12–15]. They also display complex sex-, tissue- and development-specific expression patterns which are controlled by hormones or growth factors [16], suggesting that these CYPs may have critical roles, not only in elimination of endobiotic signalling molecules, but also in their production [17]. Data from *CYP* gene disruptions and natural mutations support this view (see e.g. [18,19]).

Other mammalian CYPs have a prominent role in biosynthetic pathways. CYPs belonging to gene families 5 and 8A are involved in thromboxane and prostacyclin synthesis, CYPs from families 11, 17, 19, and 21 are required for steroid-hormone biosynthesis, CYPs from families 7, 8B, 24, 27, 46, and 51 catalyse reactions in the pathways leading to the biosynthesis of bile acid, vitamin D_3 and cholesterol and CYP26 is involved in retinoid metabolism [1,2]. These CYPs usually have selective substrate specificities and they are subject to tight tissue-specific and hormone-dependent regulation [20,21]. In addition, mutations in the structural genes for these CYPs underlie some common and severe inherited diseases [22,23].

Thus *CYP* genes are uniquely positioned (i) to respond to both endogenous and exogenous signals by changes in *CYP* gene expression, and (ii) to modulate the strength and duration of these signals and even to form new signalling molecules through CYP-mediated metabolism (Figure 1). These signalling molecules may then exert their function via the ligand-dependent nuclear receptors described below.

Overview of the nuclear receptor (NR) superfamily

The NR superfamily codes for transcription factors that transform extracellular and intracellular signals into cellular responses by triggering the transcription of NR target genes. NRs share significant similarity with classical steroid-hormone and thyroid-hormone receptors (TRs) in their DNA-binding domain (DBD)

Abbreviations used: AF-1 and AF-2, activation functions 1 and 2; AhR, aryl-hydrocarbon receptor; Arnt, AhR nuclear translocator; CAR, constitutively active receptor; CPF, *CYP7A* promoter-binding factor; CYP, cytochrome P450; DBD, DNA-binding domain; DEX, dexamethasone; DR*n*, IR*n* and ER*n*, direct, inverted and everted repeat with *n* bp spacing; ER, oestrogen receptor; FXR, farnesoid X receptor; GH, growth hormone; GR, glucocorticoid receptor; HNF-4, hepatocyte nuclear factor 4; LBD, ligand-binding domain; LXR, liver X receptor; NFI, nuclear factor I; NR, nuclear receptor; PB, phenobarbital; PBREM, PB-responsive enhancer module; PCN, pregnenolone 16α-carbonitrile; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RA, retinoic acid; RAR, retinoic acid receptor; RXR, retinoid X receptor; SF-1, steroidogenic factor 1; SHP, short heterodimerization partner; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TR, thyroid-hormone receptor; VDR, vitamin D receptor.

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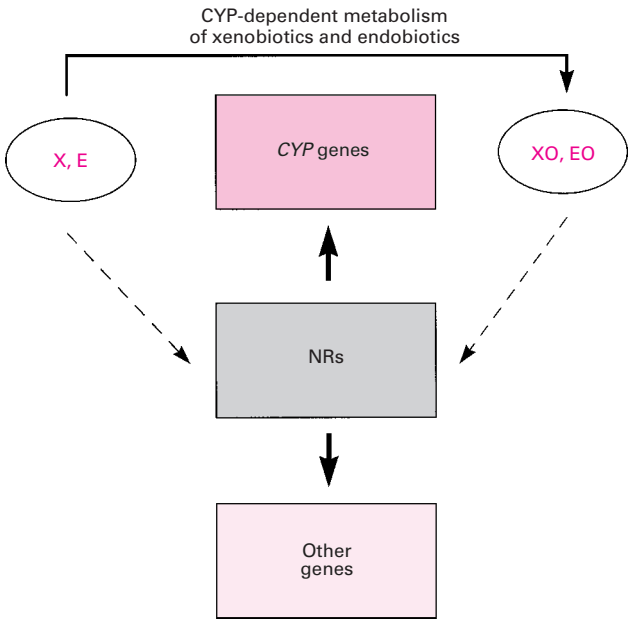

Figure 1 Relationship between NRs, their ligands and CYP enzymes

NRs (grey box) are ligand-activated transcription factors regulating (↑↓) the activity of *CYP* (mid-pink box) and other genes (pale-pink box) to generate specific cellular responses to activating ligands). These ligands are formed and degraded via specific CYP enzymes (⋯➤). The ligands may be xenobiotics, endobiotics (X, E) or their oxidation products (XO, EO).

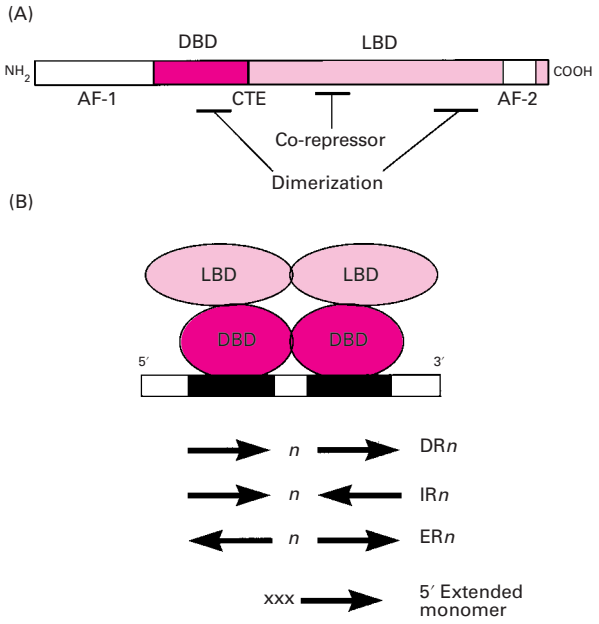

Figure 2 Structural domains in NRs and their DNA-binding sites

(**A**) The NRs display a common modular structure consisting of a DBD (red) and an LBD (pink). Imbedded in these are the C-terminal extension (CTE) often required for correct DNA binding, and the AF-2 activation core in the extreme C-terminus. NRs show great variability in their N-terminus, which in some cases harbours an independent AF-1 activation domain. (**B**) The binding of NR dimer to its cognate DNA element (black) is shown. Dimerization is indicated by the overlap in the DBD and LBD domains. The currently known orientations of NR half-sites are shown by solid arrows.

and ligand-binding domain (LBD) [24] (Figure 2A). The superfamily also contains receptors for non-steroid ligands, such as retinoid acid, prostaglandins and fatty acids [25] and so-called 'orphan' receptors, for which no physiologically relevant activators or ligands are yet known [26]. Over 70 distinct members of NR superfamily have been identified to date [27]. Distortions in structural genes of some NRs cause certain types of leukaemia and hormone-resistance syndromes [28–30].

Response element, DBD and dimerization domains

The response element of a NR is usually composed of two half-sites related to the hexamer AGGTCA. The organization of the binding site mirrors the nature of receptor binding (Figure 2B): (i) steroid-hormone receptors bind as homodimers to palindromes with a 3 bp spacing; (ii) many other hormone and orphan receptors form heterodimers with the retinoid X receptor (RXR) and bind to repeats with variable spacing; and (iii) some receptors bind as monomers to a single AGGTCA-like site [31]. In some cases, the nucleotide identity in the half-sites, in their spacer or in the 5′ extension can dramatically affect the binding specificity, affinity and/or the transactivation properties of the NR [32–34]. On the basis of crystal structures and mutagenesis of several NRs, the 70-amino-acid conserved DBD consists of two zinc-finger subdomains followed by a C-terminal extension. The amino acids around the fourth cysteine residue in the first zinc finger define the binding specificity to the response-element half-site [31,35]. The C-terminal extension is important for correct DNA binding, especially for monomeric orphan receptors and some RXR heterodimers [36,37]. The NR dimer formation is accomplished by two distinct domains, one in the DBD and the other involving helix 10 in the LBD [38–40].

Ligand-binding and activation domains

About 250 C-terminal residues constitute the LBD that also includes a region for ligand-dependent activation (activation function 2; AF-2). Currently, several crystal structures of ligand-free, agonist- or antagonist-bound LBDs are known [41]. Even though the LBD is structurally based on a similar three-layered helix fold in all NRs, the actual ligand-binding pocket shows remarkable NR- and ligand-specific variation in its size and, naturally, amino acids involved in ligand binding (e.g. [40–44]).

According to the current model of NR activation (Figure 3), ligand binding induces great structural changes in the folding of the LBD, with AF-2 being repositioned so as to form a hydrophobic patch that is accessible to common co-activators and co-integrators such as p300/CBP, SRC-1 and TIF2 [41,45,46]. Co-activators bind to ligand-bound NRs through their LXXLL repeats (e.g. [47]) and they either possess intrinsic histone acetyltransferase activity or recruit additional histone acetyltransferases that relieve suppressive effects of the chromatin to activate transcription [48]. Some, but not all, ligand-free NRs interact with co-repressors such as N-CoR and SMRT [46] to suppress gene transcription via recruitment of histone deacetylases [49]. In addition, some receptors contain a separate activation domain (AF-1) that is ligand-independent but can interact with the AF-2 region [50,51].

Regulation of NRs

The effects of an NR on target gene expression are therefore subject to regulation (and competition by other NRs) at DNA-binding-site selection, selective dimerization, binding of distinct

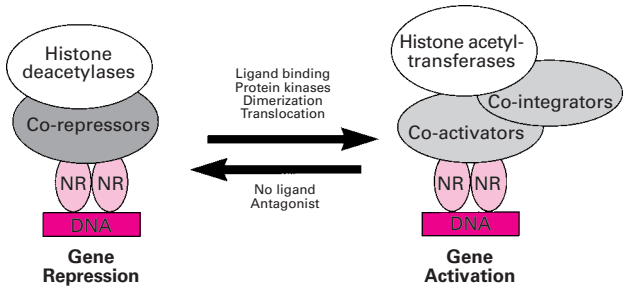

Figure 3 Model for gene activation and gene repression by NRs

Ligand binding or other activating processes induce the binding of the NR to the DNA element (red). The ligand-bound NR (pink ellipses) then recruits a complex of common and/or NR-specific co-activators and co-integrators (pale-grey ellipses), and turn on acetylation of histones to activate transcription. In the absence of ligands or upon antagonist binding, some, but not all, NRs bind co-repressors (mid-grey) to trigger deacetylation of histones and maintenance of chromatin structure in an inactive state.

ligands and selective co-activator assembly (Figure 3). In addition, several other transcription factors may compete for the same co-activators [45,46]. NR-mediated regulation may be complex in other ways as well. For example, multiple isoforms of NRs can be produced by multiple promoters or alternative splicing in a cell-specific manner [52,53]. Some NRs are predominantly cytoplasmic, being translocated to the nucleus only upon ligand binding [54,55]. Many NRs are phosphorylated either upon ligand binding or through cross-talk from other signalling systems [56,57].

NR REGULATION OF *CYP* GENES

Xenobiotic-, oestrogen- and retinoid-metabolizing CYP1 forms: potentiation and suppression of AhR-dependent expression by indirect action of steroid hormones and retinoids

CYP1A1, CYP1A2, and CYP1B1 can activate polycyclic hydrocarbons and arylamines to carcinogens and produce catechol oestrogens via 2- and 4-hydroxylation [6,58–60], reactions contributing to carcinogenesis. Polyaromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induce *CYP1A* and *CYP1B* genes through binding to the aryl-hydrocarbon receptor (AhR), translocation of the ligand-bound AhR into the nucleus, and association of the AhR with its dimerization partner, AhR nuclear translocator (Arnt). The AhR·Arnt complex then binds to xenobiotic response elements and turns on the *CYP* gene transcription in a wide variety of tissues [61]. The induction can be modulated by the protein kinase C pathway [62,63].

Glucocorticoid receptor

CYP1A1 mRNA induction is potentiated 2–4-fold by dexamethasone (DEX) in hepatic and endothelial cells [64–67]. In hepatocytes, DEX acts through intron I of the *CYP1A1* gene [68], although a direct effect of the glucocorticoid receptor (GR) has not been shown [69]. In contrast, *CYP1B1* gene induction is suppressed by DEX in fibroblasts in a GR-dependent fashion. This effect is mediated by a 265 bp DNA fragment carrying the AhR response elements, but no distinguishable GR elements [70]. Modulation of *CYP1A1* and *CYP1B1* gene expression probably takes place through protein–protein interactions between the GR and other transcription factors, as described previously [71] or by competition for common co-regulators.

Oestrogen receptor (ER)

Maximal CYP1A1 induction depends on the presence of ERα in some cell lines [72–74]. The ERα may act indirectly on cell type-specific factors, because an acute treatment with anti-oestrogens did not influence CYP1A1 or CYP1B1 expression in carefully selected ERα-positive cells. Both genes were induced by TCDD, regardless of the ERα status [75]. Conflicting results may stem from sequestration of other factors by the over-expressed ERα (= 'squelching') or from activation of ligand-free ERα by growth-factor-dependent kinases [76,77]. Cells derived from the established ERα knockout mice [78] should assist in clarification of this matter.

No oestrogen-responsive elements in the *CYP1A1* gene have been identified. A mutual competition between ERα and AhR for their DNA elements [79] has been disputed [80]. Hoivik et al. [80] also found no inhibition by oestrogen of *CYP1A1* induction in Hepa 1c1c7 or in MCF-7 cells. In contrast, a recent report indicated that ER agonists antagonized *CYP1A1* induction only in oestrogen-regulated endometrial ECC-1 and MCF-7 cells, but not in Hep3B hepatoma or in primary keratinocytes [81]. No effect of oestradiol on DNA binding by AhR nor on *CYP1B1* induction was seen, and the ERα-mediated suppression of *CYP1A1* induction was reversed by ER antagonists and by co-expression of nuclear factor I (NFI), a transcription factor interacting with both AhR and ERα [81]. AhR and ERα potentially compete for other co-regulators as well [82,83]. Such contradictory results could result from use of different cell sublines with variable (transcription) factor levels or from squelching effects. A role for ERβ that can be activated by ERα ligands [84] or for ER-related receptors [85,86] should also be considered. In conclusion, ERα seems to exert its effects on *CYP1* gene expression indirectly.

Retinoid receptors

In keratinocytes, retinoic acid (RA) has been reported either to down-regulate [87,88] or up-regulate [89] *CYP1A1* gene expression. The *CYP1A1* gene harbours an unusual DR4 element that conferred a modest RA-dependent increase in reporter-gene activity [90]. In hepatocytes, retinoids had little effect on CYP1A1 or CYP1A2 mRNAs [91], while RXR- and RA receptor (RAR)-selective ligands decreased hepatic CYP1A2 in intact animals [92]. The retinoid receptors involved, their possible interplay with the AhR, or the role of RA metabolism in these processes are not known. Mouse strains deficient in RAR and RXR isoforms [25] are available to address this problem and to elucidate the role of retinoids and CYP forms in skin physiology and carcinogenesis.

Cross-talk from AhR to NRs

The AhR and its ligands down-regulate ER-dependent gene expression in MCF-7 breast-cancer cells and in rodent oestrogen-responsive tissues [93]. Multiple mechanisms have been suggested, and probably they are cell type- and gene-specific. For example, binding of an ERα-containing complex to the cathepsin D gene promoter was abolished by AhR recognizing an overlapping site [94]. There is a potential for competition between AhR and ERα for common co-regulators [81–83]. Finally, TCDD sometimes reduced ligand and DNA binding by ERα [95,96]. CYP1A inducers seem to reduce ligand binding to GR and RARs and down-regulate peroxisome proliferator-activated receptor γ (PPARγ) mRNA, leading to decreased receptor-dependent gene expression [97–100]. AhR ligands also disturb thyroid hormone homoeostasis [101] and suppress several sex-specific CYP

mRNAs [102,103]. The nature of this general suppression of cellular functions by AhR ligands is not clear. It may reflect the limiting cellular amounts of co-activators and probably contributes to TCDD toxicity.

The disruption of *AhR* gene leads to a marked liver disease [104] and elevated hepatic levels of retinoids due to a decrease in CYP-mediated catabolism of RA [18]. Intriguingly, this defect is not due to the RA-inducible 4-hydroxylase CYP26 [18]. CYP1A enzymes are known to metabolize retinoids [105,106], and intact AhR is required for the basal expression of CYP1A2 [104]. Even though the mouse CYP1A2 does not metabolize RA [18], it may metabolize other retinoids [14], and thus the loss of CYP1A2 might contribute to retinoid accumulation in *AhR* null mice. This hypothesis could be tested in *Cyp1a2* null mice [107].

Steroid-metabolizing liver- and sex-specific CYP2A, CYP2C, CYP2D, and CYP3A forms: hepatocyte nuclear factor 4 (HNF-4) and orphan receptors contribute to basal expression and ERα governs sexual dimorphism

Members of families CYP2 and CYP3A metabolize efficiently both xenobiotics and endogenous compounds [6,7,12]. They also display complex developmental, species-dependent and sexually dimorphic patterns of regulation that may substantially differ even between closely related CYP isoforms [16]. Several P450s in this group exhibit liver-specific or liver-predominant expression driven by distinct liver-enriched transcription factors [108,109]. Intriguingly, several sex-specific and growth- hormone (GH)-dependent CYP mRNAs is suppressed by chemicals that can activate AhR or NRs [102,103,110].

HNF-4

Comparison of *CYP2A*, *CYP2C*, and *CYP2D* gene sequences indicated that many promoters contain a motif (HPF1) around −100 bp that is important for binding of HepG2-specific proteins and transcriptional activity of rabbit *CYP2C* genes [111]. The consensus HPF-1 motif (5′ RRRNCAAAGKNCANYY; see Table 1) resembled the binding site for hepatocyte nuclear factor 4 (HNF-4), an liver-enriched orphan receptor that binds to DNA as a homodimer [24,112]. *In vitro* competition and antibody supershift assays, and co-transfection of HNF-4, indicated that HNF-4 was the major regulator for rabbit *CYP2C* genes in liver [113,114]. HNF-4 or HPF-1 motifs were also shown important for activation of human *CYP2C9* [115], mouse *Cyp2a4* [116], rat *CYP3A* [117,118] and mouse *Cyp2d9* genes [119].

Orphan receptors

Related rat *CYP2C7*, *CYP2C11*, *CYP2C12* and *CYP2C13* genes seem less dependent on HNF-4 [120,121]. Although HNF-4 could recognize the HPF-1-like elements in almost every *CYP2C* gene, most of the binding in rat liver nuclear extracts was not due to HNF-4; mutation of HPF-1 motifs did not significantly reduce *CYP2C* promoter activity in HepG2 cells; and co-expression of HNF-4 in non-hepatic cells had only a marginal effect on the promoter activity [120,121]. However, the sequences of virtually all rat *CYP2C* elements do not completely conform to the HPF-1 motif or HNF-4 site [111,112], but differ at critical positions [111,114]. It appears that orphan receptors such as ear-2 and ear-3 work in concert with other transcription factors to regulate the basal *CYP2C13* gene expression [120]. The same or related orphan receptors may influence *CYP3A* gene expression as well [117,118].

Even though the activities of rabbit *CYP2C* gene promoters correlated well with their HNF-4-binding affinity, they did not correspond to CYP2C mRNA levels *in vivo* [114]. This suggests that, in addition to HNF-4, other regulators are also important. Nevertheless, the majority of the liver-specific *CYP2A*, *CYP2C*, *CYP2D* and *CYP3A* genes are regulated by HNF-4 and related orphan receptors. Small sequence variations within the binding sites may lead to distinct binding preferences and, therefore, to gene-specific regulation by various NRs.

ER

A new role for NRs in *CYP* gene transcription has recently been discovered [122]. The sex-specific transcription of *CYP2C11* and *CYP2C12* genes is regulated by sexually distinct patterns of GH secretion in the rat that can be abolished by neonatal gonadectomy or hypophysectomy [123,124]. In the male mouse, GH governs the expression pattern of *Cyp2a4* and *Cyp2d9* genes, while in the female mouse, GH has little effect [125]. The GH-elicited nuclear localization of transcription factor STAT5b in the male mouse has emerged as the major regulator of the sex-specific *CYP* gene expression [126]. The presence of a functional ERα is absolutely required for proper sex-specific expression of *Cyp2a4* and *Cyp2d9* genes in the liver [122]. Normally, STAT5b is not detectable in nuclei from female liver. Disruption of ERα leads to nuclear localization of STAT5b in females and appearance of CYP2D9 mRNA; this masculinization can be abolished by hypophysectomy. Thus ERα is probably needed for programming of the hypophysis that involves sex-dependent expression of neuronal aromatase (CYP19) [127]. The recent *Cyp19*-null mouse [128] could be useful in tackling this problem: even though ERα can be activated by mechanisms other than ligand binding [76,77], the lack of the natural ligand for ERα and ERβ should shed new light on the role of oestrogen in sexual differentiation.

Steroid- and fatty acid-metabolizing CYP2B, CYP3A and CYP4A forms: inducible expression is governed by ligand-activated nuclear receptors CAR (constitutively active receptor), PXR (pregnane X receptor) and PPARα

CYP2B genes

CYP2B is a large gene subfamily that encodes versatile catalysts of xenobiotic and steroid hydroxylation [7,129–131]. Even closely related isoforms display distinct sex- and tissue-specific regulation [132,133]. A hallmark for *CYP2B* gene regulation is the strong inducibility of some isoforms by structurally diverse xenobiotics, including industrial solvents, barbiturates, antimycotics, and pesticides [7]. These chemicals are typified by phenobarbital (PB) and they can up-regulate several hepatic enzymes involved in xenobiotic metabolism [7] and other genes as well [134]. PB induction does not require on-going protein synthesis, but it involves an okadaic acid-sensitive dephosphorylation process [135–138].

CYP2B response elements

Data from the *CYP2B2*-transgenic mice [139] and mutant rats deficient in CYP2B2 induction [140] strongly suggested that PB-responsive elements do not reside near the transcriptional start site in *CYP2B* promoters. PB-responsive primary hepatocyte cultures, *in situ* DNA injection techniques, and the availability of active and inactive derivatives of a powerful inducer, 1,4-bis-[2-(3,5-dichloropyridyloxy)]benzene [141] facilitated the discovery of PB-responsive DNA elements (PB-responsive enhancer module; PBREM). PBREM-like elements are located at around −2300 bp in rat *CYP2B2* and mouse *Cyp2b10* genes [142–144]

Table 1 Examples of interactions between *CYP* genes and nuclear receptors

Abbreviations: NSAIDS, non-steroidal anti-inflammatory drugs; MR, mineralocorticoid receptor.

CYP gene	CYP substrates/products that can serve as NR ligands	NR affected by the CYP substrate/product	NRs known to regulate *CYP* gene*	Response element†	NR effect‡	Cell specificity of NR action
CYP1A	Oestrogens, retinoids	ERs, RARs, RXRs	ER, GR RAR	Indirect DR4?	ER, GR ↑ ↓ RAR ↑ ↓	Ubiquitous Ubiquitous?
CYP1B	Oestrogens	ERs	ER, GR	Indirect	ER ↑ ↓, GR ↓	Ubiquitous
CYP2A	Androgens	AR	HNF-4	DR1	HNF-4 ↑	Hepatocytes
CYP2B	Xenobiotics§ Methoxychlor	Many	CAR (PXR)	DR4	CAR ↑	Hepatocytes
	Androgens§, oestrogens, retinoids	AR, ER, RARs, RXRs	GR	GRE half-sites?	GR ↑	Hepatocytes?
CYP2C	Xenobiotics§ NSAIDs Methoxychlor	Many	HNF-4, orphan RAR	DR1 Unknown	HNF-4 ↑, orphan ↑ ↓ RAR ↑	Hepatocytes Hepatocytes
	Androgens, retinoids, fatty acid derivatives	AR, ER, RARs, RXRs PPARs				
CYP2D	Xenobiotics§ Androgens, oestrogens, vitamin D_3	Many AR, ER	ER VDR HNF-4	Indirect Unknown DR1	ER governs GH secretion VDR ↓ HNF-4 ↑	Hypophysis Hepatocytes Hepatocytes
CYP3A	Xenobiotics§ Methoxychlor	Many	PXR (CAR) HNF-4, orphan	DR3, ER6 DR1	PXR ↑ HNF-4 ↑, orphan ↑ ↓	Hepatocytes, intestine Hepatocytes
	Androgens, corticoids, oestrogens, pregnanes§	AR, ER, GR	GR	GRE half sites?	GR ↑	Hepatocytes?
CYP4A	Fatty acid derivatives	PPARs	PPAR, (orphan)	Extended DR1	PPAR ↑, orphan ↓	Hepatocytes
CYP26	Retinoic acid	RARs, RXRs	RAR	Unknown	RAR ↑	Ubiquitous
CYP27B1	Vitamin D		VDR	Unknown	VDR ↓	Kidney
CYP24	Vitamin D	VDR	VDR (RXR, orphan)	DR3	VDR ↑, orphan ↓	Ubiquitous
Steroidogenic CYPs	Androgens, oestrogens, corticoids, pregnanes§	AR, ER, GR, MR	SF-1, orphan	Extended monomer	SF-1 ↑, orphan ↑ and ↓	Adrenals, gonads
CYP7A	Precursors for steroids		CPF LXR, FXR	Extended monomer DR4	CPF ↑ LXR ↑, FXR ↓	Hepatocytes Hepatocytes
Bile-acid-forming CYPs	Oxysterols	LXR, FXR	LXR?, FXR?	Unknown		
CYP51	Sterols		LXR	Unknown	Unknown	

* Nuclear receptors in parentheses have a tentative role.
† Binding elements related to AGGTCA motifs (? means role of the element is tentative or not clear; indirect or unknown effects described in the text).
‡ Activating (↑), repressing (↓) or conflicting (↑ ↓) effects on *CYP* gene expression.
§ Many compounds in this class are activators of PXR, CAR or PPAR.

and at −1700 bp in human *CYP2B6* [145]. Upon exposure of liver to PB, an increase in protein binding to PBREM can be detected *in vivo* and *in vitro* [146,147]. The PBREM is organized as an NFI-binding site flanked by two DR4 motifs (5′ RKGYCANNNNAGTNSA). Sequence differences between the PB-responsive *Cyp2b10* and non-responsive *Cyp2b9* genes and transgenic studies established that both NR sites contributed to the PB response, but the NFI site was not crucial [145,147–149].

Binding factors

Co-transfections in HepG2 and 293 cells showed that, among several NRs, only the CAR [150] could activate the PBREM [147]. Mutations in NR motifs or their spacing that decreased the PB response in primary hepatocytes correlated well with loss of *in vitro* binding to NR1 probe and with decreases in CAR-dependent gene activation [147]. DNA-affinity purifications indicated that both mouse CAR and RXR were enriched on *Cyp2b10* NR1 columns by prior PB treatment of mice [147]. Importantly, the mouse PXR was not detected in these fractions (T. Sueyoshi, I. Zelko and M. Negishi, unpublished work); this can be now understood by the relative weakness of PB as an activator of the mouse PXR [151]. In mouse liver, the binding of CAR and RXR to NR1 is PB-dependent and precedes the induction of CYP2B10 mRNA [147]. Furthermore, both CAR expression and *Cyp2b10* gene induction are liver-specific [152,153].

Activators of CAR

PBREM mediated the induction by structurally diverse chemicals ranging from methyl isobutyl ketone and pyridine to chlorpromazine and polychlorinated biphenyls, with excellent correlation with induction of endogenous CYP2B mRNA [145,148]. These results suggest that most, if not all, PB-type inducers converge their effects on CAR or at least on proteins binding to PBREM. Thus CAR can sense a wide spectrum of xenobiotics, and it may activate *CYP* and other genes responsible for their elimination.

Suppression of CAR by inhibitory ligands?

This inducer-dependent increase of CAR binding and activation of PBREM in hepatocytes is in contrast with inducer-independent activation of PBREM by CAR in HepG2 and 293 cells. Neither cell line can transcribe the endogenous *CYP2B6* gene in response to PB. Because co-transfected CAR can activate reporter genes without addition of ligands [150,152], one would have envisioned a mechanism to keep CAR silent in the absence of inducers *in vivo*. The identification of 3α-hydroxy, 5α-reduced androstanes as inhibitory ligands that can dissociate co-activators from CAR [154] suggested a clear-cut mechanism: inducers could either displace or prevent formation of steroids that repressed CAR. Indeed, when HepG2 cells were transfected with a CAR expression vector, the endogenous *CYP2B6* and transfected PBREM-reporter genes became activated, suppressed by 3α-androstenol, and re-activated in 3α-androstenol-treated cells by PB [145]. These results show that CAR is the PB-inducible regulator of *CYP2B* genes.

However, the IC_{50} for 3α-androstenol suppression was much higher than its levels in the blood [155]. Unlike the co-expression of many NRs and their ligands [156], 3α-androstenol is produced in testis, where CAR and CYP2B10 mRNAs are absent [152,153]. Production of 3α-androstenol in hepatocytes has not been demonstrated, and it is possible that the true inhibitory ligand for CAR is a related, more potent steroid. Several compounds that deplete cellular sterols are also CYP2B mRNA inducers, and addition of hydroxylated cholesterol can suppress PB induction [157]. This agrees with the idea that primary hepatocytes can synthesize a sterol/steroid metabolite that attenuates PB induction of *CYP2B* genes.

Suppression of CAR by cytoplasmic localization?

An alternative mechanism to suppress CAR has recently been provided. In HepG2 cells, CAR spontaneously resides in the nucleus as shown by transfection of a green fluorescent protein–CAR fusion protein [158]. The nuclear CAR was constitutively active, and its repression by 3α-androstenol did not affect its localization [158]. In primary hepatocytes, native CAR resided in the cytoplasm and was translocated in the nucleus only after the administration of inducers. Furthermore, the translocation and DNA binding of CAR could be inhibited by okadaic acid [158], an inhibitor of Ser/Thr protein phosphatases, at concentrations known to suppress *Cyp2b10* gene transcription [136]. These results indicate that the mechanism to induce *CYP2B* gene transcription might occur through activation of dephosphorylation-sensitive translocation of CAR. Such ligand-induced nuclear translocation has been shown for other NRs [55,159]. Hyperphosphorylation is often associated with decreased nuclear translocation of the NR [56]. In this scenario, CYP2B inducers would trigger the release of CAR from cytoplasmic proteins, either indirectly or through ligand binding. The latter possibility is more likely, since nuclear CAR can be activated by inducers in 3α-androstenol-treated HepG2 cells. If the conformation of CAR that is compatible with transactivation is also required for translocation, then inhibitory ligands can still keep CAR in an inactive form in the cytoplasm.

CYP3A genes

CYP3A enzymes are very active in steroid and bile acid 6β-hydroxylation and oxidation of scores of xenobiotics [5,6,160]. Because of their wide substrate specificity and prominent expression in liver and gut, they are the most important group of enzymes involved in drug metabolism [161]. Some CYP3A forms display sex- and development-specific expression [16,162] and inducibility. For example, rat *CYP3A23*, rabbit *CYP3A6*, and human *CYP3A4* genes are activated by a wide variety of antibiotics, barbiturates and other drugs, glucocorticoids and anti-glucocorticoids, and pesticides in a species-specific manner [163,164].

CYP3A response elements

The DNA elements responsive to induction by DEX have been located in the proximal promoters of *CYP3A* genes, upstream of the HNF-4 binding site [117,163,165–167]. The rat *CYP3A* genes contain a DR3 (direct repeat with 3 bp spacing) motif (5′ AGTTCANNNAGTTCA) at −130 bp and an ER6 (everted repeat with 6 bp spacing) motif (5′ TGAACTNNNNNNAGGTCA) at −160 bp. The rabbit *CYP3A6* and the human *CYP3A* genes contain only the ER6 motif in the proximal promoter, while both DR3 and ER6 are present in a strong distal enhancer in the *CYP3A4* gene at −7.7 kbp [168]. Unusually for an NR, the same factor seems to bind both DR3 and ER6 elements, although data from Huss et al. [166] indicated that mutations that destroyed the ER6 motif but created a DR4 or DR3 motif increased the response to DEX. Studies by Blumberg et al. [169] indicated that DR3 and DR4 were preferred over DR5.

Binding factors

The cloning of the mouse PXR [170] led to the discovery that not only glucocorticoids, but also antiglucocorticoids such as pregnenolone 16α-carbonitrile (PCN), activated the PXR, matching the profile of known CYP3A inducers. The mouse PXR could bind to and transactivate the rat *CYP3A* DR3 motif in response to natural and synthetic pregnanes [170]. Later on, the identification of human PXR/SXR/PAR-1 [151,169,171], its ability to bind to both ER6 and DR3 motifs, and their co-expression with CYP3A isoforms strongly indicated that PXR can regulate *CYP3A* genes.

PXR ligands

Both human and mouse PXR can activate reporter genes in response to many steroids, antimycotics and antibiotics. The species-specific induction of CYP3A forms by, for example, rifampicin or PCN [163] can now be explained by their ability to activate only the human or mouse PXR, respectively [151,169,171]. This selective ligand binding can be understood by relatively low amino acid conservation in the LBD between the mouse and human PXR. Therefore PXR may be a wide-specificity receptor for both steroids in general and xenobiotics, although the possibility of a potent endogenous ligand has not been ruled out.

Cross-talk to CAR and PXR

The DNA binding preferences of CAR and PXR are quite similar, so it is possible that these NRs may activate both *CYP3A* and *CYP2B* genes. CAR can transactivate the *CYP3A4* ER6 [145]. The contribution of PXR to CYP2B induction is unknown, but rat *CYP2B1* gene is inducible by PB in intestine [173], where PXR is more abundant than CAR [150,152,170].

DEX, a ligand for mouse PXR [170], can induce CYP2B forms in hepatocytes [136,174]. However, DEX does not activate CAR [147] or PBREM in primary hepatocytes, and PXR was not detected in NR1-affinity-purified fractions (P. Honkakoski, T. Sueyoshi, I. Zelko and M. Negishi, unpublished work). Apparently, CAR does not bind DEX, and PXR does not significantly bind to PBREM *in vivo*. These data agree with findings that rat *CYP2B* and *CYP3A* gene induction by PB and DEX proceed by distinct mechanisms [151,175]. Some overlap in CAR and PXR targets may exist, but the establishment of relative roles of CAR and PXR in induction of *CYP2B*, *CYP3A* and other genes *in vivo* awaits detailed studies on their DNA- and ligand-binding preferences, and ultimately, the generation of *CAR*- and *PXR*-null mice.

DEX may act on *CYP2B* genes through another site. A functional GR element has been described in the *CYP2B2* gene at -1350 bp [176], but its role in regulation of *CYP2B* genes is not known. Similarly, human *CYP3A5* and rat *CYP3A1* contain elements in their upstream regions that can bind the GR and transactivate in response to DEX [177,178]. Because DEX can synergize the induction by PB and PCN [65,179], these elements could work in concert with PXR. Another explanation for synergism could be the increase of PXR mRNA by DEX [180]. It should be borne in mind that DEX or glucocorticoids are required for expression of other *CYP* genes and for the maintenance of hepatocytes [7,65,69,136], so the DEX effects may not be gene-specific but rather depend on maintenance of the overall transcription capacity.

Thyroid hormone has been reported to suppress PB induction of *CYP2B* and *CYP3A* genes [7,181]. The actual targets are not known, but thyroid hormone does not influence PBREM activity [182]. The effects of retinoids on *CYP2B* and *CYP3A* gene expression are inconclusive [91,92]. The 25-hydroxycholesterol that suppressed *CYP2B* induction [157] can also activate liver X receptors (LXRs) [172], which may then interfere with CAR signalling. Some orphan receptors seem to bind to the same elements as PXR [117,118]. SHP (short heterodimerization partner) is a liver-enriched NR lacking a DBD which has been reported to suppress CAR-mediated transactivation [183]. Its role in *CYP2B* gene induction has not been studied, but a specific role seems unlikely, because the promiscuousness of SHP [183,184].

CYP4A genes

CYP4A isoforms are active in ω-hydroxylation of fatty acid derivatives such as arachidonic acid, prostaglandin A, and other eicosanoids, while they have less activity towards xenobiotics [15,185]. Their expression in liver and kidney can be increased by industrially used phthalate esters, lipid-lowering fibrate drugs, and other chemicals which share the property of being peroxisome proliferators [185,186].

Binding factors

The factor activated by peroxisome proliferators is PPARα [187]. PPARα was characterized before the binding elements responsible for induction of *CYP4A* genes were discovered. Mice lacking PPARα are refractory to induction of genes encoding *CYP4A* and other fatty-acid-metabolizing enzymes, peroxisome proliferation and carcinogenesis [188]. Two other PPAR isoforms (PPARδ and PPARγ), with distinct tissue specificities and functions, are also known [189].

Response element

The binding and activation of *CYP4A* promoter by PPARα has been well studied in rabbit *CYP4A6* [190]. This gene harbours several PPAR sites, among which a cluster of four imperfect AGGTCA motifs at around -660 bp constitutes the major response element. The motifs 2 and 3 are organized as a typical PPAR$\alpha \cdot$RXR DR1 element (where DR1 is a direct repeat with 1 bp spacing), similar to that in rat *CYP4A1* gene [191]. Both binding affinity and specificity of PPAR$\alpha \cdot$RXR for the *CYP4A6* DR1 motif were improved by 5′-flanking sequences that are conserved in other PPAR-responsive genes (5′ AWCTRGGNCANAGKTCA). The extra 5′ nucleotides seem to decrease the binding of RXR$\cdot$RXR dimers and other NRs [192] that have affinity for the single DR1 motif [193]. With use of natural PPAR response elements, it was established that the 5′ extension sequence of AWCT is crucial for PPARα and PPARγ binding and transactivation [34]. A less strict dependence on the 5′ extension was found in a PCR-based binding-site-selection study [194]. The similarity of PPAR response elements to the binding sites of monomeric NRs [36] indicates that the C-terminal extension of the PPARα DBD can discriminate among different response elements to generate a specific cellular response [37].

PPAR ligands

In addition to peroxisome proliferators, endogenous compounds such as fatty acids, leukotriene B_4 and 8(*S*)-hydroxyeicosatetraenoic acid bind to PPARα [195–197]. The ligand specificity of PPAR isoforms seems to be distinct, but overlapping, e.g. several prostaglandins activate all PPARs [197], PPARα and

PPARδ isoforms are activated by fatty acids [198], and non-steroidal anti-inflammatory drugs prefer PPARα and PPARγ [199]. Species-specific ligand binding for PPARα has been described as well [200,201]. This broad ligand specificity of PPARs can now be understood by the large ligand-binding pocket and unique ligand access cleft in PPARγ [44]. It is again possible that the function of PPARα is to sense a wide spectrum of low-affinity ligands.

Cross-talk to PPARα

The PPARα-dependent expression is also subject to cross-talk by other NRs expressed in liver such as TAK1, LXR, TR and PPARδ [202–205] and possibly by other DR1-recognizing receptors such as ARP-1 and HNF-4 [193]. The mechanisms seem to involve competition for both binding sites and common co-activators and 'inactive' heterodimer formation. *In vivo* induction of *CYP4A2* gene was suppressed by physiological levels of thyroid hormone, while that of *CYP4A1* and *CYP4A3* required higher doses [206].

The co-expression of *CYP4A* genes and PPARα [190] and data from *PPARα*-null mice [207] indicate that other PPAR isoforms do not regulate *CYP4A* genes in the liver. However, there is some PPARα-independent expression of *CYP4A* genes in *PPARα*-null mice [208]. Both PPARα and PPARγ are able to activate the *CYP4A6* promoter in transient transfections [209]. Thus it is conceivable that other PPAR isoforms may regulate other *CYP4A* genes with similar binding sites as well. CYP4A substrates often are PPAR ligands [189], so it is not unreasonable to look for PPAR-dependent *CYP4A* (or other *CYP*) genes in tissues involved in lipid metabolism.

Retinoid-metabolizing CYP forms: synthesis by CYP1A and retinoid-inducible catabolism by CYP26 and CYP2C7

Retinoids are a group of vitamin A derivatives that have profound effects on cell growth and differentiation [25,210]. They utilize two distinct NR signalling pathways, the RARs and the RXRs, which bind to DR2/DR5 and DR1 response elements respectively. RARs and RXRs are thought to be activated by all-*trans*-RA and 9-*cis*-RA respectively [31], although additional ligands are being found.

Formation of retinoids

RAs are synthesized from vitamin A by sequential reactions involving alcohol dehydrogenases or short-chain dehydrogenases, aldehyde dehydrogenases and several CYP isoforms [14]. CYP2B and CYP2C isoforms primarily convert retinoids into presumably inactive 4-hydroxy derivatives while rabbit CYP1A forms can catalyse both RA formation and 4-hydroxylation [105,106,211]. CYP2J4 also produces RA [212]. Novel 4-oxo acid and aldehyde derivatives are also powerful and abundant RAR ligands [213,214], and they may be produced by CYP1A2 [106].

Catabolism of retinoids

A novel RA 4-hydroxylase gene, *CYP26*, is highly expressed in liver and brain and present in several cell lines [215,216]. CYP26 mRNA is induced by RA via action of RAR$\gamma \cdot$RXRα heterodimers through as-yet-undefined DNA elements [217]. Because of its RA-dependent regulation and wide expression, CYP26 is thought to control the level and the activity of RA [215,217]. However, this form is highly specific to all-*trans*-RA, so elimination of other active retinoids requires the action of other CYP enzymes. This view is supported by the fact that the presence of CYP26 cannot prevent accumulation of retinoids in *AhR*-null mice [18]. Of interest are the known RA and retinol 4-hydroxylases, rat CYP2C7 and human CYP2C8 [211,218,219]. Rat *CYP2C7* gene is down-regulated by vitamin A deficiency and up-regulated by retinoids through the RAR pathway [220,221]. Intriguingly, all-*trans*-RA-dependent induction could be abolished by the CYP inhibitor ketoconazole, and 4-oxo-RA was an inducer of CYP2C7 mRNA [221]. This controlled regulation by retinoids suggests a special role for CYP2C7 in hepatic retinoid metabolism. The site of RAR action and its potential interplay with HNF-4 and orphan receptors [120] on *CYP2C7* promoter are yet not known.

Vitamin D-metabolizing CYP forms: synthesis by CYP27A1 and CYP2D25, and vitamin D-inducible catabolism by CYP24

Vitamin D is a precursor for biologically active 1α,25-dihydroxyvitamin D_3, which has a central role in regulation of calcium homoeostasis and cell differentiation [21,222]. The 1α,25-dihydroxyvitamin D_3 binds to the vitamin D receptor (VDR), VDR$\cdot$RXR heterodimer then binds to DR3 elements present in target genes and it activates their transcription via AF-2- and co-activator-dependent mechanisms [223,224]. Some VDR targets such as genes for parathyroid hormone and *CYP27B1* are down-regulated, but the ability of VDR to bind co-repressors or to interfere with positively acting transcription factors is not yet resolved [21,225]. Formation of VDR homodimers and interplay with thyroid-hormone signalling has been suggested [226], but their physiological role has not yet been established. With respect to CYP forms not involved in vitamin D metabolism, CYP3A4 mRNA is induced by 1α,25-dihydroxyvitamin D_3 in Caco-2 cells [227], although the direct binding of VDR to the *CYP3A4* promoter or its DR3 element have not been established.

Formation of 1α,25-dihydroxyvitamin D_3

1α,25-Dihydroxyvitamin D_3 is formed by 25-hydroxylation in liver and 1α-hydroxylation in kidney. The first reaction can be catalysed by CYP27A1, the mitochondrial sterol 27-hydroxylase [228,229]. Biochemical studies and evidence from CYP27-deficient patients suggested that another microsomal CYP form is the physiologically more important 25-hydroxylase [21]. This was supported by the fact that *CYP27A1*-null mice have normal plasma levels of 1α,25-dihydroxyvitamin D_3 [230]. The cloning of the microsomal 25-hydroxylase rather unexpectedly indicated that this form is CYP2D25 [231]. This emphasizes again that CYPs in families 1–4 have important physiological functions. The 25-hydroxylation can be suppressed by 1α,25-dihydroxyvitamin D_3 by an unknown mechanism [232].

1α-Hydroxylation is catalysed by renal CYP27B1 which is down-regulated by 1α,25-dihydroxyvitamin D_3 and tightly regulated by other factors [21,233]. The down-regulation does not take place in *VDR*-null mice [233]. No distinct VDR response elements in *CYP27B1* genes have yet been identified. The mouse *CYP27B1* -1.7 kbp promoter was unresponsive [234], while elements within the -1100 bp of the human *CYP27B1* gene mediated activation by parathyroid hormone that was reduced by 1α,25-dihydroxyvitamin D_3 [235,236].

Catabolism of 1α,25-dihydroxyvitamin D_3

The mitochondrial 1α,25-dihydroxyvitamin D_3 24-hydroxylase, *CYP24* is a well-characterized vitamin D target gene [237].

CYP24 inactivates vitamin D to calcitroic acid [238]. The critical role for CYP24 in vitamin D catabolism was proved by generation of *Cyp24*-null mice which exhibited hypercalcaemia and abnormal bone histology [21,239]. The *CYP24* gene is expressed in many vitamin D target tissues, and it is up-regulated by its substrate through VDR·RXR-dependent binding to two conserved response elements at about −300 bp and at −150 bp [240,241]. Retinoids can increase *CYP24* gene expression by RAR·RXR binding to VDR response elements [242]. The orphan receptor TR4 which is co-expressed with VDR can down-regulate *CYP24* expression [243].

Steroidogenic CYP forms: complex tissue-specific and cAMP-inducible expression is controlled by steroidogenic factor 1 (SF-1) and gene-specific regulators

Steroid hormones are important endocrine factors that regulate sexual differentiation and maintenance, ion balance and carbohydrate and lipid metabolism. Steroid hormones act through their classical ligand-activated receptors, which in turn modify the expression of their target genes [24].

Tissue-specific expression

Steroid hormones are produced from cholesterol via the action of six CYP enzymes (CYP11A, CYP11B1, CYP11B2, CYP17, CYP19, CYP21), aided by 3β- and 17β-hydroxysteroid dehydrogenases [244]. These CYPs are expressed in a cell-specific manner. For example, adrenal cortex that produces gluco- and mineralocorticoids, but not oestrogen, expresses all but the *CYP19* gene, and oestrogen-forming ovary expresses *CYP11A*, *CYP17* and *CYP19* genes [20,244]. Also brain, adipose tissue, placenta and some fetal tissues express selected steroidogenic CYPs, probably reflecting a local requirement for hormones [244–246].

The expression pattern of *CYP* genes correlates with that of the SF-1 [247,248]. SF-1 is an orphan receptor that binds to extended AGGTCA-like half sites (5′ YCAAGGYC or RRAGGTCA) present in all steroidogenic *CYP* proximal promoters [247,249]. Mutation of these SF-1 binding sites can decrease the *CYP* promoter activity in cells of adrenal or gonadal origin [32,250–254]. SF-1 also directs the organogenesis of adrenals and gonads, because *SF-1*-null mice lack these organs [247,255]. Oxysterols were found to activate the SF-1 [256], but their role in physiological regulation of CYPs has been questioned [257,258]. SF-1 activates genes through AF-2 [259] and p300/CBP co-regulators [260].

SF-1 is not the sole cell-specific regulator of steroidogenic *CYP* genes, because adrenals or gonads that express SF-1 lack CYP19 or CYP21 and CYP11B mRNAs respectively. This idea is reinforced by findings that CYP11A mRNA is present in placenta, skin, and hindgut of *SF-1*-null foetuses [246,261] and that mRNAs for several CYPs, but not SF-1, are detectable in several brain regions [245]. Contribution of other NRs that have affinity for SF-1 binding sites [32,85,262,263] or unrelated factors [264,265] requires further studies.

Cyclic AMP-induced expression

The steroidogenic *CYP* genes are positively regulated in response to trophic peptide hormones through activation of cAMP pathway [266]. Several studies have indicated SF-1 as one cAMP target for *CYP11B1*, *CYP11A*, *CYP17* and *CYP19* genes [250,252,253,259,267,268]. However, SF-1 confers only a partial cAMP response, indicating a need for other transcription factors [250,268] such as Sp1 [253,260,269]. For example, corticotropin (ACTH) induces binding of another orphan receptor that binds to the SF-1 site at −65 bp, resulting in increased *CYP21* gene transcription [32]. Other regions of the *CYP21* gene seem to contribute to the cAMP response [270]. Loss of trophic hormones down-regulates steroidogenic CYP levels without affecting SF-1 [271]. Recently, phosphorylation of SF-1 by mitogen-activated kinases was suggested to confer maximal transactivation [51]. There is no clear evidence for increased up-regulation or phosphorylation of SF-1 in response to trophic hormones, with the possible exception of CYP19 regulation [267,268]. Therefore cAMP-dependent regulation probably requires factors unique to each steroidogenic *CYP* gene.

Cholesterol-metabolizing CYP forms: bile acid synthesis is controlled by ligand-activated LXR, farnesoid X receptor (FXR) and a liver-specific receptor

Cholesterol synthesis and CYP51

The metabolism of cholesterol is regulated at the biosynthetic pathway by oxysterols that prevent activation of SREBP family of regulators [272]. The biosynthetic pathway involves only one CYP enzyme, the lanosterol 14α-demethylase CYP51 [273]. CYP51 produces so-called meiosis-activating sterols [274] that can activate LXRα [275] and possibly the ubiquitously expressed LXRβ [172] as well. The human CYP51 mRNA was suppressed by oxysterols in HepG2 and adrenal cells [276], while the rat CYP51 was induced by gonadotropin in the ovary [277], reminiscent of steroidogenic CYP regulation. Both mechanisms are currently unknown, but may involve NRs.

Cholesterol disposal, CYP7A and CYP7B

The level of cholesterol is controlled also by catabolism to bile acids [278]. Bile acids are formed from cholesterol via two routes. The first is the liver-specific 7α-hydroxylation catalysed by CYP7A [279] which is down-regulated by the ultimate product chenodeoxycholic acid and activated by dietary cholesterol [278,280]. The second route involves CYP7B, the oxysterol 7α-hydroxylase that is expressed predominantly in brain and liver [281,282]. The substrates for CYP7B can be produced at least by sterol 27-hydroxylase CYP27A1 [228,229], a brain-specific 24(*S*)-hydroxylase CYP46 [283] and a non-CYP cholesterol 25-hydroxylase [284].

The up-regulation of CYP7A activity by excess cholesterol involves the liver-predominant LXRα receptor. LXRα could be activated by several oxysterols, including the 24(*S*)-OH derivative [275]. LXRα could bind to, and activate, the *CYP7A* promoter via the DR4 motif at −74 bp, while the related LXRβ was not able to bind to DR4 well [285]. The DR4 motif is contained within the proximal of the two elements crucial for the bile acid response [286]. These findings were confirmed by the report that *LXRα*-null mice could not up-regulate their *Cyp7a* gene when challenged with high dietary cholesterol levels [287].

The tight liver-specificity of *CYP7A* gene expression cannot be determined by LXRα alone. A liver-specific nuclear receptor, CYP7A-promoter-binding factor (CPF) [288], was shown to bind and activate the *CYP7A* promoter. The monomeric AGGTCA-like binding site at −136 bp for CPF is contained within the second of the bile acid response elements identified by the Chiang group [286,288]. This suggests that both CPF and LXRα are needed for *CYP7A* gene regulation. Interestingly, CPF is very similar to SF-1 [247,288]. Because some oxysterols can activate SF-1 [256], it is conceivable that CPF and LXRα regulate *CYP7A* gene expression in parallel in response to oxysterols.

The third part of *CYP7A* regulation, the suppression by bile acids, is also being unravelled. First, the disruption of the *Cyp27a* gene and subsequent decrease in bile acid synthesis leads to a compensatory up-regulation of CYP7A mRNA [230]. Secondly, bile acids such as chenodeoxycholic acid have now been established as ligands for FXR [289,290], an NR expressed mainly in liver and kidney [33,291]. The ligand-bound FXR will suppress the *CYP7A* gene, as expected from *in vivo* studies. On the other hand, it can activate the gene for bile-acid-binding protein [292] or reporter genes driven by heterologous promoters [290]. LXRα-mediated transcription from the original LXR DR4 motif [33] can be repressed by ligand-bound FXR [290], suggesting a direct communication between the two receptors. It is not yet known by which mechanism the FXR-mediated suppression occurs. FXR could interfere also with CPF [288] or with other NRs potentially binding to *CYP7A* promoter [293], although the role of the latter proteins in *CYP7A* gene expression is disputable.

Oxysterol-forming CYP27A1 and CYP46 forms

CYP27A1 catalyses several hydroxylation reactions on the cholesterol side chain [228,229,294]. The regulation of this form has not been studied in detail, but rabbit CYP27A1 was up-regulated by cholesterol [295], while the effects of bile acids point towards down-regulation [296,297]. The function of CYP46 is the removal of extra cholesterol from the brain [298] via production of the 24(*S*)-OH derivative [283]. The presence of LXRβ in the brain and its activation by the 24(*S*)-OH cholesterol suggest a potential activation mechanism for *CYP46* gene that remains to be tested.

Bile acid-forming CYP8B and other CYP forms

CYP8B constitutes a further step in bile acid synthesis by catalysing liver-specific 12α-hydroxylation [278]. CYP8B mRNA is suppressed at the pretranslational level by thyroid hormone [299] and up-regulated by bile acid sequestration, concomitant with CYP7A mRNA increase [300]. Further metabolism of bile acids by side-chain and 6β-hydroxylation are catalysed by CYP3A and CYP2B enzymes [131,160] that are regulated by PXR and CAR. The above reports suggest that similar NR-dependent mechanisms that control *CYP7A* gene expression may also regulate other enzymes involved in cholesterol and bile acid metabolism. Results testing this hypothesis should be forthcoming.

CONCLUSIONS

Feedback regulation

As detailed in previous sections, the *CYP* genes and nuclear receptors form a complex network that may involve feedback regulation (see Figure 1 and Table 1). First, several CYPs degrade ligands that activate the NR responsible for regulation of this specific CYP form, thus creating a direct feedback loop. Clear examples of this can be recognized in CYPs metabolizing vitamin D (CYP24 and VDR) and retinoids (CYP26, CYP2C7 and RAR). PPARα-, PXR- and CAR-activated *CYP4A*, *CYP3A* and *CYP2B* genes fall into this category: fatty acids and steroid hormones serve as ligands for PPARα and PXR which in turn increase ligand elimination by CYP4A-mediated ω-hydroxylation [185] and CYP3A-catalysed 6β-hydroxylation respectively [170]. Methoxychlor activates CAR and stimulates its own metabolism by CYP2B [145,301]. Candidates for this class might include CYP2A isoforms which are stereospecific androgen 7α-hydroxylases [302], present in testis and liver that are sites for androgen production and elimination respectively. Secondly, steroidogenic, vitamin D (CYP2D25) and cholesterol-metabolizing CYPs produce ligands for major classes of NRs, but the immediate CYP product is not a ligand for the suppressor. Instead, a more complex loop, either through the pituitary via action of trophic hormones (e.g. sex steroids and CYP17, CYP19, sex-specific hepatic CYPs) or through suppression by ultimate products (e.g. bile acids and CYP7A), is employed. Thirdly, some CYPs may ensure a steady elimination of a wide range of endobiotics or xenobiotics. This is made possible by prominent basal and liver-specific *CYP* gene expression that is controlled by HNF-4 or related orphan receptors. Certain CYPs in gene families *CYP2A*, *CYP2C*, *CYP2D* and *CYP3A* belong to this class. For these, no activating ligand or feedback loop are evident. However, they may be indirectly suppressed by CYP inducers or NR ligands (e.g. [102,103,110]).

Formation of NR ligands

In addition to the above feedback regulation, CYPs can often produce metabolites that act as ligands for unrelated NRs. Especially in the case of xenobiotics, this can result in production of potential disruption of cellular homoeostasis. For examples, CYP1A2 and CYP2C19 enzymes form oestrogenic metabolites from methoxychlor [303], and a metabolite of PPARα ligand can activate the PPARγ [201]. In addition, inefficient removal of xenobiotics by CYPs may disrupt NR signalling (e.g. [93,98–100]. In the case of endobiotics, production of such 'unrelated' ligands may be less frequent, but formation of LXRα-activating sterols by CYP51 and CYP46 and retinoid formation by CYP1A may be such instances, and the androgen action in the brain is mediated by the CYP-dependent metabolism to oestrogen and ERα [122,127]. More details of this interwoven regulation and metabolism of *CYP* genes by endobiotics and xenobiotics are clearly needed.

The past decade has brought new evidence that enhances the role of CYP enzymes as active participants in the control of cellular homoeostasis, instead of passive, low-specificity enzymes for general chemical elimination. CYP enzymes are involved in regulation of cellular levels of many endocrine and intracrine compounds that act via nuclear receptors. The regulatory triangle involving ligands, CYPs and nuclear receptors is completed by recent findings that ligand-activated nuclear receptors are responsible for the expression of major classes of CYP enzymes.

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