PREGNANE AND XENOBIOTIC RECEPTOR (PXR): A PROMISCOUS XENOSENSOR IN HUMAN HEALTH AND DISEASE

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SUMMARY

Pregnane and Xenobiotic Receptor (PXR) is a member of the nuclear receptor super-family of ligand-regulated transcription factors. Some of its key roles in normal physiological controls and patho-physiological situations are recently becoming more apparent. PXR responds to a large range of chemically distinct endobiotics (steroids, bile acids and their derivatives, vitamins, etc.) and xenobiotics (synthetic drugs, herbal medicines, endocrine disruptors, etc.). As a result of its chemical sensory capabilities and gene modulatory functions in controlling cellular detoxification pathways, PXR has been appropriately termed by some as a 'xenosensor' or 'master regulator'. The present review focuses on two facets of this unique receptor. First, its function in maintaining homeostasis that primarily involves rapid and timely elimination of toxic endogenous metabolites and exogenous chemicals. Second, its involvement in dysregulated metabolic conditions (such as osteomalacia) and certain chronic diseases like cancer. When PXR encounters circumstances that are discordant with normal homeostasis, it orchestrates a response by utilizing and modulating the components of the central detoxification defense machinery, i.e. phase I and phase II drug metabolizing enzymes, as well as drug transporters. The presence of PXR in tissues other than the expected ones (liver and intestine) along with the occurrence of various isoforms (three or more) indicates much more diverse roles for this receptor than previously suspected. The possibility of the presence of various PXR isoforms in different tissues suggests utilization of combinatorial mechanisms to regulate different sets of genes under varied physiological and pathogenic conditions. Further studies are expected to divulge important roles of PXR in drug-drug interactions, development of several metabolic disorders and in designing safer therapeutic molecules.

Keywords: Cancer, cytochrome P450, metabolic disorders, nuclear receptor, SXR

INTRODUCTION

Incessant exposure to xenobiotics via multiple routes, either by ingestion, inhalation or absorption, necessitates operation of coordinated and tightly regulated mechanisms for maintaining homeostasis. Genes encoding for cytochrome P450 (CYP) enzymes and several other conjugating enzymes and transporters are considered to be the primary components of our innate defense system against multiple chemical insults (1). Among the CYP family, CYP1A, CYP2B, CYP3A and CYP4A subfamily members respond promptly upon xenobiotic challenge (2). Notably, members of the CYP3A subfamily are of prime importance since these not only display a broad substrate specificity but are also involved in the metabolism of a large number of synthetic medicines that are currently available (3, 4). Importantly, a diverse range of foreign chemicals with varied structural features also induce CYP3A family members, in turn providing an adaptive response for enhanced xenobiotic clearance. A detrimental aspect of CYP3A induction is that it also mediates potentially life-threatening drug-drug interactions where one drug (CYP3A inducer) accentuates the metabolism of a second drug that is a substrate for CYP3A (5). Hence, elucidation of the molecular mechanisms underlying the induction of CYP3A was vital for the development of safer medicines. This paved the way for the discovery, identification and characterization of a novel constituent of the body's xenobiotic defense system, the Pregnane and Xenobiotic Receptor (PXR; NR1I2).

In 1997, a mouse sequence encoding for a novel nuclear receptor (NR) first appeared in the Washington University's express sequence tag (EST) database and, subsequently, was identified and cloned primarily based upon its sequence homology with other nuclear receptors (6). This novel receptor protein was named PXR, based on its activation by C21 steroids (pregnanes) including pregnenolone 16α-carbonitrile (PCN), which is a classic inducer of CYP3A in rats and mice (6). Subsequently, the human PXR was independently cloned by three groups (7-9) and was alternatively referred to as Steroid and Xenobiotic Receptor (SXR) or Pregnane-Activated Receptor (PAR). Likewise, rat, rabbit, monkey, dog and fish PXR were also cloned. Also, a closely related receptor from chicken was cloned and termed 'Chicken Xenobiotic Receptor' (CXR) (10). To avoid ambiguity, the terms Pregnane X Receptor or Pregnane and Xenobiotic Receptor have been appropriately retained (9, 11).

To date 48 nuclear receptors (NRs) have been identified in humans. On the basis of their ligand status, these NRs have been broadly divided into two groups.

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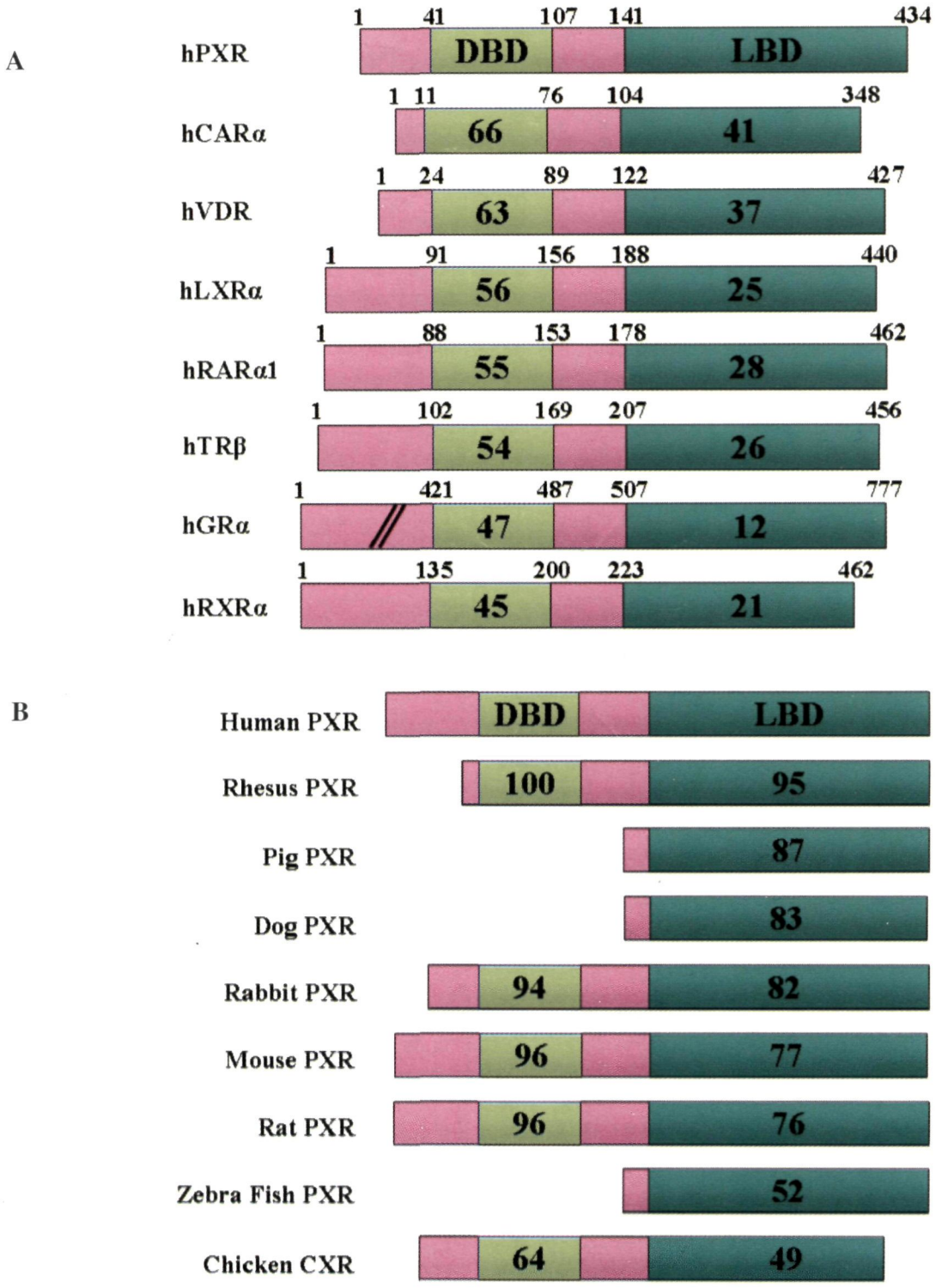

Fig.1.(A) Sequence comparison of human PXR with other members of nuclear receptor super-family. The similarity is expressed as percentage of amino acid identity in DNA binding domain (DBD) and ligand binding domain (LBD) of human PXR. **(B)** Comparison of sequence similarity of human PXR with other species. The similarity is expressed as percentage of amino acid identity in the DNA binding domain (DBD) and ligand binding domain (LBD) of human PXR.

The first group of receptors for classical endocrine hormones includes glucocorticoid, mineralocorticoid, progesterone, estrogen, androgen, thyroid hormone, vitamin D and all-trans retenoic acid receptors. The ligands for these receptors were documented as important endocrine hormones long before their receptors were discovered. The second group of nuclear receptors comprises peroxisome proliferator activated receptors, farnesoid X receptor, liver X receptor, constitutive androstane receptor, PXR and others that are collectively referred to as 'orphan nuclear receptors' (12, 13). This group includes all the receptors for which physiological ligands were not known at the time of their cloning. PXR, like other members of the nuclear receptor super-family, shares common domain structures that include an amino-terminal domain, a central DNA binding domain (DBD) and a carboxyl-terminal ligand-binding domain (LBD). Among the nuclear receptors, the amino-terminal domain is highly variable both in terms of length and amino acid sequence and it contains an activation function-1 helix (AF-1). The DBD is ~70 amino acid residues long and is highly conserved. It consists of two zinc fingers, each composed of four cysteine residues that chelate a zinc atom. The LBD is ~250 amino acid residues long and folds to form a hydrophobic pocket into which the ligand binds (Fig. 1A). In addition to its ligand binding properties, the LBD also contains dimerization and transcriptional activation motifs, including the well-characterized activation function-2 (AF-2) helix in the extreme C-terminal portion of the LBD (14). The ligands for NRs are small and lipophilic in nature, which permits them to diffuse into cells and interact with the LBD of the receptor. The binding of the ligand to the LBD results in a conformational change in the AF-2 that disrupts interactions with transcriptional co-repressor proteins such as N-CoR and SMRT and allows interactions with transcriptional co-activator proteins such as the SRC-1 family members (15). Upon activation by ligand, the activated PXR, as a hetero-dimer with RXR, is capable of binding to specific motifs (DR-3, DR-4, DR-5, ER-6 and ER-8) with remarkably different architectures in the xenobiotic response elements (6, 8, 16-19). Each motif comprise two copies of the consensus nuclear receptor binding site AG(G/T)TCA and the two binding sites are organized either as a direct repeat with a spacer of 3 to 5 nucleotides or as an everted repeat with a spacer of 6 or 8 nucleotides. The PXR/RXR complex, upon binding to specific response elements, stimulates the expression of target genes.

ROLE OF PXR IN XENOBIOTIC DETOXIFICATION

A diverse set of chemicals including, synthetic drugs (e.g., the antibiotic rifampicin, the glucocorticoid dexamethasone, the anti-glucocorticoid RU486, the anti-fungal clotrimazole, the diabetes drug troglitazone and the anti-estrogen tamoxifen, etc.), pesticides (pretilachlor, metolachlor, bupirimate, oxadiazon), endocrine disruptors (phthalic acid, nonylphenol) and other environmental contaminants (polychlorinated biphenols) have been shown to activate PXR in cell-based reporter assays, scintillation proximity assays (SPA) or co-activator receptor ligand assays (CARLA) (20). A list of major PXR ligands (hormones, herbal and prescription medicines) that activate PXR is represented in Table 1. It is conceivable that PXR functions as a low affinity, broad specificity receptor for many endogenous molecules such as glucocorticoids, estrogens, bile acids, oxysterols, etc. Each of these molecules, at normal physiological concentrations, utilizes only their specified high affinity receptors i.e., glucocorticoid receptor (GR), estrogen receptor (ER), farnesoid X receptor (FXR) and liver X receptor (LXR), respectively, to modulate gene expression (21). However, when concentrations exceed normal physiological levels (stress induced levels of glucocorticoids, glucocorticoid levels in Cushing's syndrome, bile acids in cholestasis, etc.), the defense machinery becomes operational under these circumstances and each of these ligands activate PXR to induce their own metabolism, transport and elimination, so that physiological levels for these molecules can be reverted to normalcy (21). Alternatively, in circumstances such as pregnancy, levels of PXR are reported to be augmented as an adaptive mechanism to combat the high levels of circulating endocrine hormones (22).

The X-ray crystallographic analysis of the PXR LBD, both in the presence and absence of ligands, provided important insights into the molecular basis for its promiscuous behavior. Like other nuclear receptors, the PXR LBD is composed of 12 alpha - helices that fold to form a hydrophobic pocket in the lower portion of the protein. However, several unique features in the PXR LBD appeared to distinguish it from the other members of nuclear receptor super-family. The volume of the PXR ligand-binding pocket is >1,300Å^3 (Angstron unit -)which is significantly larger in size as compared with the ligand binding pockets of other nuclear receptors. The large volume is due to the presence of two additional strands of beta-sheet that are not found in other nuclear receptors. Also, the PXR LBD is unique in terms of its smooth and elliptical shape. The combination of a large volume and smooth shape appears to produce the broad substrate specificity of PXR (13). Furthermore, unlike other nuclear receptor orthologs, PXR orthologs share less amino acid identity in the LBD, providing the possibility for marked variation in its activation profiles across species (23) (Fig. 1B). Thus, activation of PXR coordinately stimulates the expression of a network of genes involved in the phase I, phase II and phase III metabolism of xenobiotics (24, 25). In phase I, the major reaction involved is hydroxylation, catalyzed by a class of enzymes referred to as monooxygenases or cytochrome P450s (CYPs).

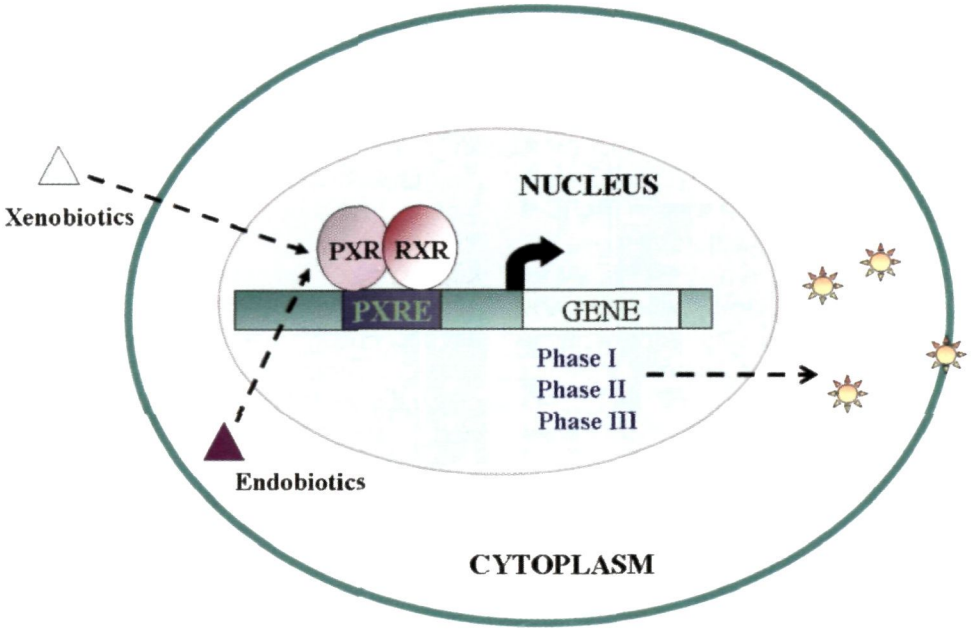

Fig. 2. A simplified model to demonstrate the regulatory role of PXR in the endobiotic and xenobiotic defense system. PXR, upon activation by several xenobiotics and endogenous metabolites, heterodimerizes with RXR and activates the expression of genes involved in phase I, phase II and phase III metabolism. This results in increased metabolism and elimination of the activating ligand from the cellular milieu.

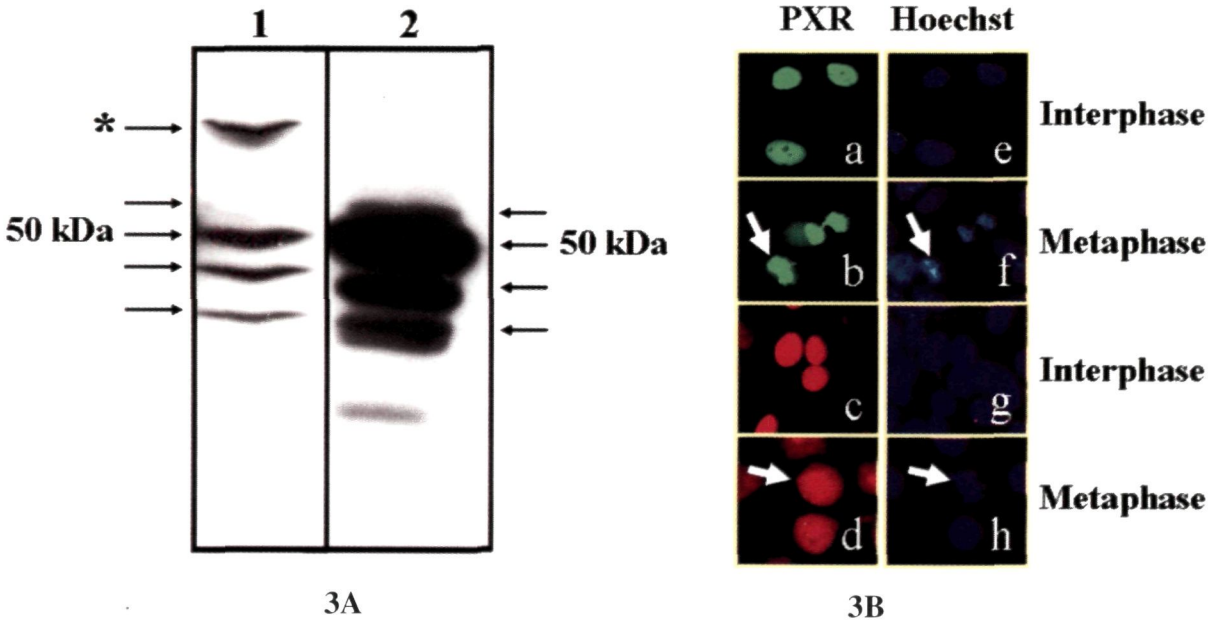

Fig. 3. (A) Detection of PXR isoforms. In western blot analysis, endogenous PXR isoforms are detectable in a lung cancer cell line, A549 (lane 1) and in a PXR transfected COS-1 cell line (lane 2). The major 50 kDa PXR band and its other potential isoforms have been previously described (11). The relevance of an extra band in A549 cells, shown with an asterisk, is not clear. **(B)** GFP-tagged and immunologically detected untagged PXR during interphase is a nuclear protein (left panel, a and c). During mitosis (metaphase indicated by arrows) PXR associates with condensed chromosomes (b and d). Right panel (e to g) shows the corresponding Hoechst-stained nuclei / condensed metaphase chromosomes (28).

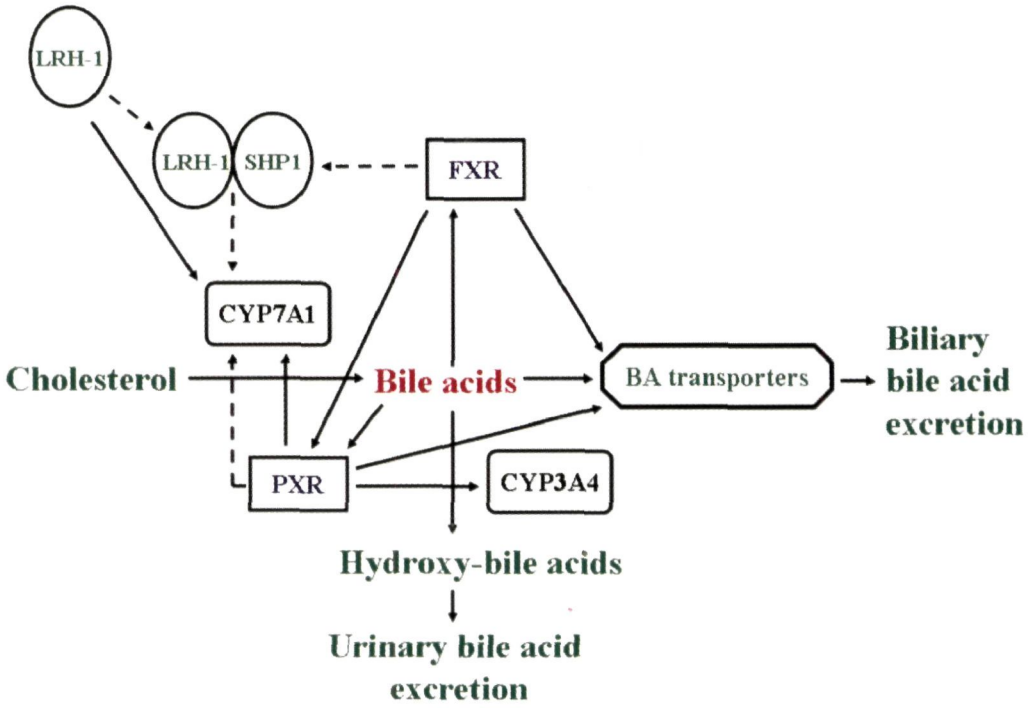

Fig. 4. PXR functions as a bile acid sensor and maintains bile acid homeostasis. The principal bile acid sensors, PXR and FXR, upon activation by circulating levels of bile acids, modulate the expression of genes involved in bile acid biosynthesis and transport. Activated FXR suppresses CYP7A1 indirectly by inducing the expression of SHP. SHP then heterodimerizes with LRH-1 and interferes with LRH-1 induced CYP7A1 expression. It also mediates the induction of PXR. Activated FXR and PXR stimulate the expression of bile acid transporters directly and, hence, both receptors augment the excretion of bile acids into bile. In addition, PXR induces CYP3A expression, which in turn hydroxylates the bile acids enhancing their urinary excretion. PXR also mediates the basal expression or repression of CYP7A1. Receptor-mediated feedback regulation of bile acids is indicated by dotted arrows and feed-forward regulation by solid arrows.

Members of the CYP3A sub-family (mainly CYP3A4) are responsible for metabolizing more than 50% of all drugs, and its inducible expression through PXR activation plays a pivotal role in the clearance of a number of endogenous as well as exogenous xenobiotic compounds. In phase II, the phase I derivatives are converted to various polar metabolites by specific enzyme-mediated conjugation with glucuronic acid, sulfate, acetate or glutathione or by methylation. During phase III metabolism, the resultant water-soluble (polar) compounds are eliminated from the cellular milieu (Fig. 2). Further, in a recent attempt to identify PXR targets, the human genome was screened for potential PXR binding sites by using in-silico based approaches (26). Among the identified targets, approximately 281 genes were reported to be involved in metabolism, 97 genes in transport and several more were reported to mediate a variety of other cellular processes. Additionally, with 55 allelic variants and three major splice variants PXR (PXR-1, encodes a protein with 434 amino acid residues; PXR-2, encodes a protein containing 473 amino acid residues with 39 additional amino acid residues at the NH_2 terminal end; PXR-3 encodes a protein containing 397 amino acid residues with an internal deletion of 37 amino acid residues in LBD) were reported recently (11, 21, 27). Taken together, variation in the expression levels of PXR isoforms, combined with their differential transcription potentials, is expected to have important implications on tissue-specific, as well as inter-individual target gene expression profiles (27). A novel observation with PXR is its association with the condensed chromosomes during all the stages of mitosis (28). If this behavior has any repercussion in orchestrating defensive events through chromosomal condensation and segregation or 'gene book-marking' is a matter of conjecture (29). Figure 3A reveals the presence of three endogenous PXR isoforms in a lung cancer cell line while figure 3B shows a typical association of PXR with mitotic chromosomes.

Although PXR appears to have evolved as a part of a broader protective response against xenobiotics, including prescription medicines and several other foreign chemicals, its activation critically mediates important

drug-drug interactions. Activation of PXR by therapeutic molecules could mediate the subsequent induction of a major constituent of cytochrome P450, such as CYP3A, and also several other genes of the xenobiotic defense system and, hence, result in accelerated metabolism of co-administered drugs. In the present era of poly-pharmacy, in which patients are administered multiple medications, this phenomenon raises serious health concerns (30). Appreciating that the activation of PXR and its induction of CYP3A is a common cause for drug-drug interactions should aid in replacing some of the current therapeutic molecules with safer medicines that do not activate PXR (5).

ROLE OF PXR IN BILE HOMEOSTASIS

Bile acids, produced by the liver, are essential for the absorption of dietary lipids, fat-soluble vitamins and their synthesis from cholesterol provide a means for eliminating excess cholesterol from the body. Bile acid homeostasis is under stringent control since these endogenous detergents can be extremely toxic if retained in the body at elevated levels. A major form of defense against toxic bile acids is provided by a member of nuclear receptor super-family, farnesoid X receptor (FXR; NR1H4). In humans, FXR is activated by the principle bile acids, cholic acid, chenodeoxycholic acid and by their taurine and glycine conjugated derivatives (31). When activated, FXR regulates the expression of genes involved in bile acids biosynthesis and transport. FXR stimulates the expression of intestinal bile acid binding protein and the bile salt export pump directly (32) while it suppresses CYP7A1 (which catalyzes the rate-limiting step in the classical pathway for the conversion of cholesterol to bile acids) expression indirectly by inducing the expression of short heterodimer protein (SHP). SHP then hetero-dimerizes with liver receptor homolog-1 (LRH-1) and interferes with LRH-1 induced CYP7A1 expression. Thus, FXR mediates both feed-forward and feed-back regulation of bile acid homeostasis (23). Also, FXR-null mice did not show repression of CYP7A1 and exhibited elevated levels of bile acids in the serum and, interestingly, in these mice the level of CYP3A11 in the liver was increased dramatically, indicating the existence of an adaptive mechanism to combat the toxic effects from enhanced levels of bile acids (33). Currently, the role of PXR in the regulation of CYP3A11 (human CYP3A4 ortholog) is evident. A series of bile acids were tested for their ability to bind and activate PXR in cell-based reporter assays and scintillation proximity assays. Surprisingly, the secondary bile acid, lithocholic acid (LCA), and its 3-keto metabolite were able to activate human and mouse PXR (34, 35). In subsequent studies, PXR was shown to regulate several genes involved in bile acid metabolism and excretion (18, 25, 34, 36). Hence, it is reasonable to propose that PXR constitutes a second line of defense against the accumulation of toxic bile acids. In support to this, individuals suffering from cholestasis have elevated urinary levels of 6-hydroxylated bile acids, including the LCA metabolite hyodeoxycholic acid, which are produced by CYP3A4. Thus, 6-hydroxylation appears to be an adaptive mechanism for reducing the levels of toxic bile acids in humans (36, 37). Furthermore, data from PXR-null mice confirmed the role of PXR in the regulation of both the basal expression and repression of CYP7A1 (through a distinct mechanism from FXR) and other genes that are implicated in bile acid metabolism. These include, multi-drug resistance-associated protein 2 (MRP2) and organic anion transporting polypeptide 2 (OATP2) which transport bile acids across hepatic canalicular and sinusoidal membranes, respectively, and CYP3A which hydroxylates bile acids including LCA (Fig. 4) (18, 34, 36). Indeed, in one of the recent reports, PXR was identified as a target of FXR. The report suggests that bile acid activated FXR can concurrently block synthesis of bile acids and also induce PXR, contributing to enhanced clearance of bile acids. The coordinated activity of FXR and PXR eventually constitutes an efficient mechanism for protection against bile acid-induced liver damage (38).

Certain therapeutic drug molecules, which are known to activate PXR in cell-based reporter assays, including rifampicin, St. John's wort (SJW) and ursodeoxycholic acid have been used successfully to treat some hepatic disorders including cholestasis (39). Although the molecular basis of their anti-cholestatic effects has remained obscure, accumulated evidence confirms the role of PXR in bile acid metabolism and excretion and the findings that these therapeutic compounds activate PXR in turn suggest that their anti-cholestatic effects may be mediated in part through the activation of this nuclear receptor. These observations provide the possibility that the selective PXR activators, either alone or together with FXR agonists, may have therapeutic utility in the treatment of biliary cholestasis (39).

ROLE OF PXR IN BONE METABOLISM

Vitamin D is essential for the maintenance of calcium homeostasis and for the development and maintenance of bones. In the liver, due to the action of two 25-hydroxylases (the mitochondrial CYP27A and the microsomal CYP2R1) the precursors of vitamin D are transformed into 25-hydroxy vitamin D [25(OH) D], the major form of vitamin D in the circulation (40). In the kidney, 25(OH) D is further hydroxylated at the 1 alpha position by CYP27B1 to form 1alpha 25-dihydroxy vitamin D [1alpha, $25(OH)_2$ D]. This biologically active form of vitamin D, then, enters the blood and reaches its target tissues, including intestine, bone, kidney, parathyroid and others (41). 25(OH) D can also be metabolized to 1 alpha, $25(OH)_2$ D

in a wide variety of tissues including colon, prostate, breast and skin where it acts as an autocrine or paracrine hormone. In the target tissues it interacts with its specific nuclear receptor, the vitamin D receptor (VDR; NR1I1) and forms heterodimers with RXR. This complex bind to specific vitamin-D-responsive elements (VDREs) and transactivates target gene expression which result in various physiological effects including calcium / bone metabolism, cell growth / maturation, and renin and insulin production (42). Once it accomplishes its functions, 1 alpha, $25(OH)_2$ D induces its own degradation via VDR-RXR, by enhancing the expression of CYP24. It catalyzes the hydroxylation of 1alpha, $25(OH)_2$ D on carbon-24 and initiates a cascade of hydroxylation and oxidation events leading to the formation of water-soluble and biologically inactive calcitrioic acid which is eventually excreted into bile.

Chronic use of phenobarbital, phenyton, rifampicin, carbamazepine, glucocorticoids and anti-retroviral drugs can induce abnormalities in calcium, vitamin D andbone metabolism that ultimately may result in defective bone mineralization (42). Furthermore, a common characteristic that is shared by these diverse medications is the induction of hepatic cytochrome P450s which are involved in either hepatic endobiotic and / or xenobiotic metabolism. Hence, the induction of hepatic cytochrome P450s is thought to potentiate the metabolism of vitamin D, ultimately leading to vitamin D deficiency. Further attempts to explore the influence of these diverse medications on individual CYPs, involved in regulating vitamin D levels (CYP27A, CYP2R1, CYP27B1 and CYP24), highlight the role of CYP24 in drug-induced osteomalacia (43). Identification of a promiscuous xenobiotic receptor, i.e. PXR, led to the speculation that the drug-induced adverse effects might be mediated in part through this novel member of nuclear receptor super-family. In subsequent molecular investigations, the PXR-RXR heterodimeric complex has been shown to recognize the VDREs of CYP24, which is primarily responsible for the elimination of 1 alpha, $25(OH)_2$ D (43). Also, PXR-mediated induction of

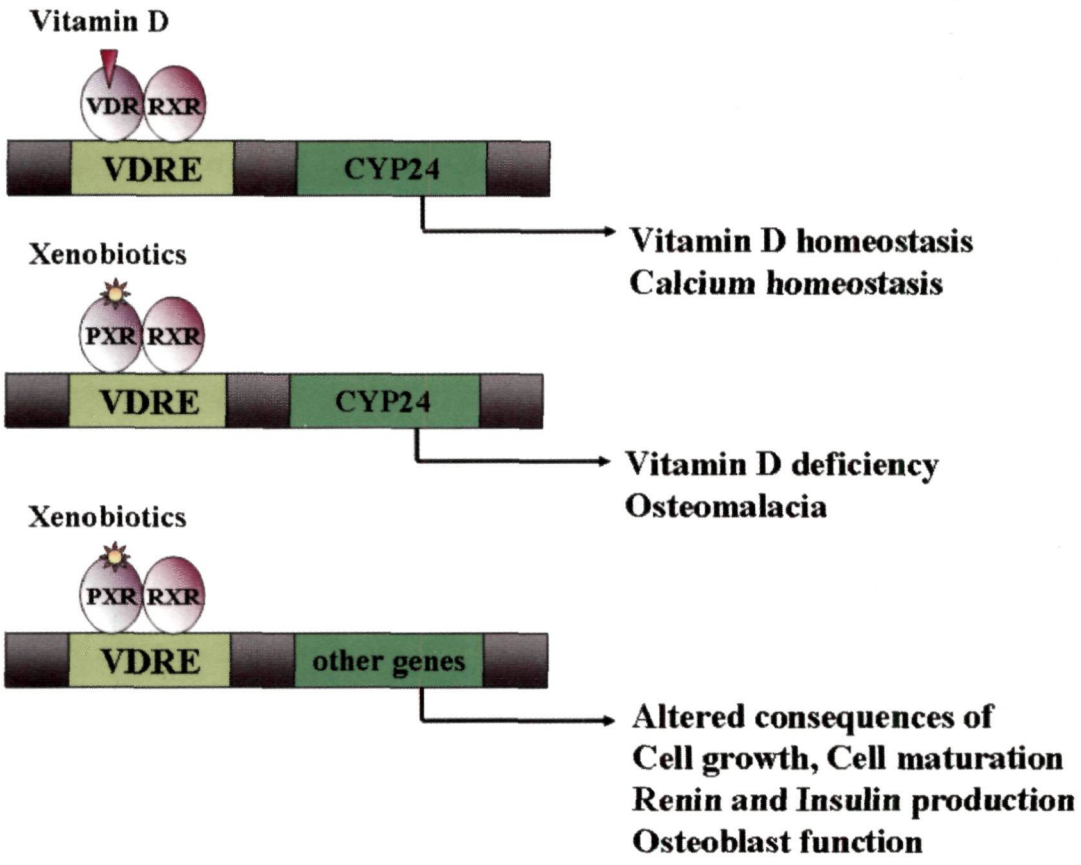

Fig. 5. Xenobiotics that activate PXR perturb vitamin D function and metabolism. In target tissues, the biologically active form of vitamin D, 1 alpha, $25(OH)_2$ D, activates its specific nuclear receptor VDR. Activated VDR heterodimerizes with RXR and modulates gene expression involved in calcium homeostasis. Also, 1 alpha, $25(OH)_2$ D regulates its own levels *via* down-regulation of the vitamin D biosynthesis enzyme, CYP27B, and by up-regulation of the vitamin D catabolism enzyme, CYP24. Drugs that activate PXR accelerate vitamin D catabolism *via* up-regulation of CYP24, leading to vitamin D deficiency and eventually osteomalacia. In addition, with the activation of VDERs in other VDR-regulated genes, PXR regulators tend to interfere with certain vitamin D regulated events.

Table 1: A list of principal molecules that activate PXR

Drug	Therapeutic Property	Reference(s)
Artemisinin	Anti-malarial	56
Cholesterol	Essential for functioning of all human organs	7
Clotrimazole	Anti-mycotic	9
Corticosterone	Anti-inflammatory	8
Cortisol	Anti-inflammatory	8
Curcumin	Anti-malarial, Anti-oxidant, Anti-inflammatory	57
Cyproterone acetate	Anti-androgen	9
Dexamethasone	Anti-inflammatory	9
Dihydrotestosterone	Androgen	8
Docetaxel (Taxotere)	Anti-cancer	58
Ecteinascidin	Anti-cancer	58
Estradiol	Estrogenic	59
Forskolin	Fat burning	60
Glutethimide	Sedative	61
Guggulsterone	Lowers cholesterol	62
17α -hydroxy-progesterone	Contraceptive	59
Hypericin	Anti-depressant	63
Hyperforin	Anti-depressant	63
Kaempferol	Anti-oxidant, Anti-fatigue	63
LGD1069 (targretin)	Anti-cancer	59
Lovastatin	Anti-hypercholestrolemic	9
Luteolin	Anti-diabetic, Anti-inflammatory	57
Metyrapone	Diagnosis aid	64
Mifepristone (RU486)	Abortifacient	9
Myricetin	Anti-oxidant, Anti-tumor	63
Nicotine	Pshychoactive and addective drug	65
Nifedipine	Anti-anginal, Anti-hypertensive	7
Paclitaxel	Anti-cancer	58
Phenobarbital	Sedative, Anti-convulsant	59
Pregnenolone	C21 steroid	6
Progesterone	Contraceptive	6, 9
Quercetin	Anti-inflammatory, Anti-cancer	63
Rifampicin	Antibiotic	8
Ritonavir	HIV protease inhibitor	66
Rutin	Anti-inflammatory, Anti-oxidant	63
Scopoletin	Anti-inflammatory, Anti-histamine	63
Soy Isoflavone	Anti-oxidative, Anti-hemolytic	57
St. John's wort	Anti-depressant	67
Spironolactone	Anti-hypertensive	9
Tamoxifen	Anti-cancer	68
Trans-nonacholor	Pesticide	59
Troglitazone	Anti-diabetic	59
Zearalenone (Mycoestrogen)	Oral contraceptive	69

CYP3A4 is shown to potentiate the clearance of 1α, $25(OH)_2$ D (44). Taken together, these findings represent a classical example of nuclear receptor cross-talk and suggest that the PXR activators might also interfere with VDR-controlled diverse physiological processes (Fig. 5). Thus, it is reasonable to speculate that xenobiotics and drugs causing vitamin D deficiency through PXR activation can augment the risk of several diseases that have been associated with vitamin D deficiency (42, 45).

ROLE OF PXR IN CANCER

In general, PXR is believed to be expressed primarily in liver and intestine, the tissues where maximum detoxification of noxious compounds occurs. However, the expression of PXR in certain malignancies, including breast and endometrial carcinoma has been reported recently (46-48). The significance of PXR expression in these malignancies remains somewhat unclear. As evident from the literature, PXR appears to play a dual role in the malignancies that in turn are dependent on the type of tissue involved and the cellular environment that is associated with it. PXR as a bile acid sensor, offers protection from the toxic effects of these compounds, which otherwise appears to promote cancer in colon (49). In contrast, in prostate cancer cells, it is probably involved in nullifying the protective effect mediated by vitamin D (42, 50).

Importantly, PXR is abundantly expressed in breast cancer cell lines that lack the expression of the estrogen receptor (ER) (46). Similarly, PXR up-regulation combined with ER down-regulation was identified in endometrial cancer (47). Therefore, despite the concerns relating to ER down-regulation, PXR, by inducing the synthesis of steroids locally, appears to provide an advantage to the growth of these neoplastic cells (47, 51). Indeed, PXR is implicated in sensitizing cells to oxidative cellular damage and in regulation of two crucial apoptosis inhibitor proteins, Bcl-2 and Bcl-xl. These combinatorial events may permit the cells to propagate with damaged DNA which eventually transforms them into malignant state (52, 53). Furthermore, in several cancerous cell types, PXR-mediated induction of xenobiotic metabolizing enzymes especially CYP3A4, as well as certain transporters, i.e. MDR1, is evident (54). Hence, the fact that some anticancer drugs such as paclitaxel and cisplatin activate PXR, provides a possible explanation for their reduced clinical efficacy (Fig. 6) (16).

In the light of functional cross-talk between PXR and other nuclear receptors, PXR may modulate the general or local expression profile of xenobiotic or endobiotic metabolizing enzymes (43, 55). Subsequently, this may influence the treatment regimen and prognosis of malignancies with altered consequences.

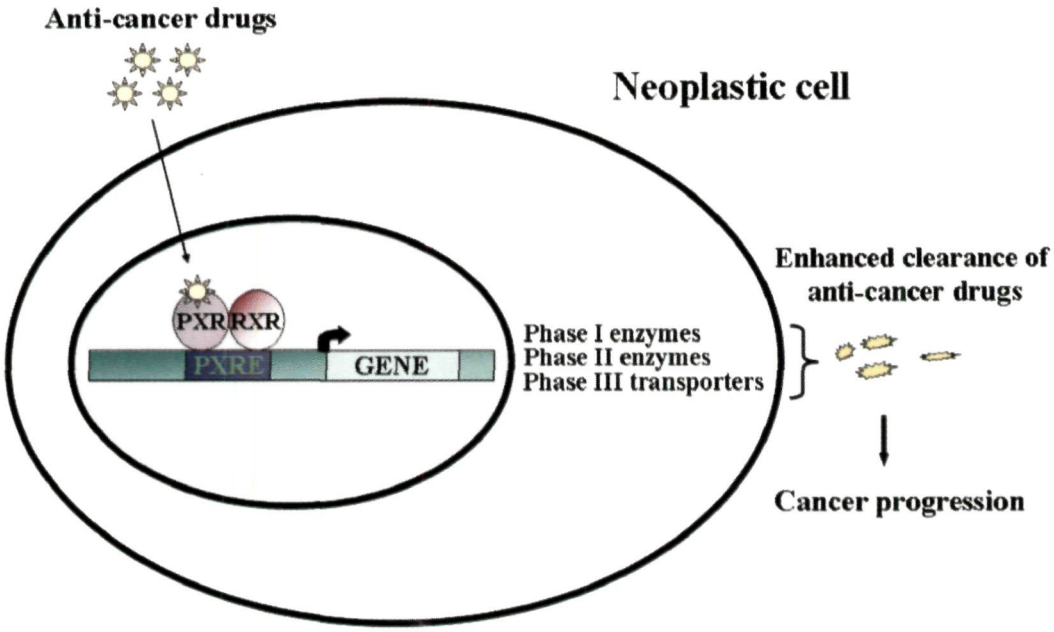

Fig. 6. A model depicting how anti-cancer drugs that activate PXR may modulate cancer progression. PXR, upon activation by anti-cancer drugs, heterodimerizes with RXR and induces the expression of phase I and phase II drug metabolizing enzymes and phase III drug transporters. Consequently, the administered chemotherapeutic compound is metabolized and eliminated from the cellular milieu. Rapid clearance of anti-cancer drugs, consequently, results in reduced clinical efficacy of the therapeutic drug and favor cancer progression.

CONCLUSION AND FUTURE PERSPECTIVES

PXR appears to have evolved to confer protection against exogenous as well as endogenous chemical insults. PXR has been shown to regulate a critical member of the detoxification system, the CYP3A family, which is involved in the metabolism of a significant number of prescription drugs. Subsequently, its extended role in regulating an entire network of genes involved in xenobiotic detoxification has been well demonstrated. This provides additional advantages to our body in combating toxic influences from intermediary metabolites that are generated during detoxification. Although PXR appears to have evolved to furnish an innate protection to our body, its low affinity and diverse substrate specificity is prone to mediate potential drug-drug interactions. Life-threatening consequences may arise if a drug that activates PXR results in accelerated metabolism of another co-administered drug. In the current era of poly-pharmacy, where patients are administered multiple medications, this phenomenon is of a serious concern. These observations necessitate development of therapeutic compounds that do not activate PXR. Furthermore, PXR, in association with FXR, appears to constitute an ideal protection system against several of the bile acids and their toxic metabolites. Hence, development of selective PXR agonists alone or in combination with FXR agonists may have utility in the treatment of cholestasis. In this direction, the ongoing molecular investigations are beginning to unravel the role of PXR in the development of disease states like drug induced osteomalacia, cancer, etc. Additionally, PXR's functional cross-talk with another member of nuclear receptor superfamily, VDR, has been shown to induce vitamin D deficiency and, hence, interferes with diverse VDR-controlled physiological processes. This potentially increases the risk of several diseases including osteomalacia, diabetes, multiple sclerosis, rheumatoid arthritis, hypertension and cardiovascular diseases. The differential up-regulation of PXR in certain cancerous conditions and subsequent identification of PXR-induced expression of xenobiotic metabolizing enzymes and drug transporters are also expected to impart a role to PXR in the prognosis of certain malignancies. Therefore, further investigations in the near future are expected to delineate extended roles of this promiscuous receptor in several human diseases and their treatments.

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