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Role of pregnane X receptor in chemotherapeutic treatment

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Abstract

Pregnane X receptor (PXR) is a member of the nuclear receptor superfamily that differently expresses not only in human normal tissues but also in numerous types of human cancers. PXR can be activated by many endogenous substances and exogenous chemicals, and thus affects chemotherapeutic effects and intervenes drug–drug interactions by regulating its target genes involving drug metabolism and transportation, cell proliferation and apoptosis, and modulating endobiotic homeostasis. Tissue and context-specific regulation of PXR contributes to diverse effects in the treatment for numerous cancers. Genetic variants of PXR lead to intra- and inter-individual differences in the expression and inducibility of PXR, resulting in different responses to chemotherapy in PXR-positive cancers. The purpose of this review is to summarize and discuss the role of PXR in the metabolism and clearance of anticancer drugs. It is also expected that this review will provide insights into PXR-mediated enhancement for chemotherapeutic treatment, prediction of drug–drug interactions and personalized medicine.

Keywords

PXR; Pharmacogenomics; Chemotherapeutic drugs; Metabolism

PXR and its pharmacogenomics

Introduction

Belonging to the NR1I subfamily of nuclear receptors (NRs), pregnane X receptor (PXR), also referred as the steroid and xenobiotic receptors (SXR) or pregnane-activated receptor (PAR), was first cloned in 1998 [1–3]. Recent studies have revealed that PXR expresses not only in human normal tissues such as liver, small intestine, colon, kidney, ovary, breast, prostate, mononuclear blood cells, placenta, bone marrow, spinal cord, stomach and heart, but also in carcinoma tissues such as breast cancer, ovary cancer, endometrial cancer, colon cancer, prostate cancer and osteosarcoma [4, 5]. The expression levels of PXR are significantly different between normal and neo-plastic tissues [4, 5]. The basic expression of PXR exhibits marked individual variations, even in the same kind of neo-plastic tissues [5].

Originally recognized as a xenobiotic sensor, PXR holds an extremely large and flexible ligand-binding pocket, allowing the accommodation of numerous structurally diverse ligands that include many endobiotics, prescription drugs, environmental pollutants, herbal medicines and dietary supplements such as bile acid, cholesterol, estrogen, progesterone, 17-hydroxypregnenolone, 5-α-pregnan-3, 20-dione, rifampicin, clotrimazole, ritonavir, cyclosporin, tamoxifen, paclitaxel, troglitazone, bisphenol A, organochlorine pesticides, multijoint bromobenzene, flame retardants, St John's Wort (SJW), gugulipid, kava kava, Sweet Wormwood Herb, Schisandra, liquorice and so on [6, 7]. Inside the nucleus, PXR forms a heterodimer with the retinoid X receptor (RXR) and binds to xenobiotic responsive

elements located in the promoter of its target genes [8, 9]. Upon ligand binding, the LBD (ligand-binding domain) of PXR went through a conformational change that facilitates the recruitment of co-activators or co-repressors, depending on the agonistic or antagonistic nature of the ligand, and alters the transcription of its target genes, thereafter [10–12] (Fig. 1). To coordinate the adaptive response against xenobiotic challenges, PXR regulates the transcriptional expression of numerous phase I and II drug-metabolizing enzymes and drug transporters such as CYP (Cytochrome P450 enzyme) 3A, CYP2B, CYP2C, aldehyde dehydrogenase, alcohol dehydrogenase, carboxylesterase, UGT (UDP-glucuronosyltransferase) 1A1, sulfotransferase, MDR (multidrug resistance gene) 1, ABCC (ATP-binding cassette transporter C) 2 and OATP (anion-transporting polypeptide) 2 [13–20]. In addition to the prototypical xenobiotic sensing effects, recent evidence has evolved PXR into an endobiotic sensor that impacts energy homeostasis and the pathogenesis of metabolic disorders [7], proinflammatory cytokines and inflammatory bowel disease [21], as well as cell proliferation, apoptosis and tumor development [22–24].

Genetic variants of PXR and their functional consequences

The PXR gene, located in chromosome 13q12-13.3, consists of nine exons and stretches approximately 37 kilo bases. To date, many PXR allelic variants have been identified in different ethnic populations [7, 25]. Among the reported 70 single nucleotide polymorphisms (SNPs) of PXR, 15 are nonsynonymous mutation in the coding regions, including four SNPs between the N terminal and the DNA-binding domain [A12T, E18K (PXR*9), P27S (PXR*2) and G36R (PXR*3)], three variants located in or near the DNA-binding domain [R98C (PXR*5), R122Q (PXR*4) and K109N] and eight variants in the LBD district of PXR [V140 M (PXR*10), R148Q (PXR*6), Q158K, D163G (PXR*11), A370T, C379G, R381 W and I403 V] [14]. Although the functional consequences are not fully illustrated, a number of SNPs are reported in the intron and promoter region of PXR gene, respectively [7].

Notably, altered expressions and activities of the PXR target genes might be associated with mutated PXR compared with the wild-type PXR. A PXR SNP at −566A > C is significantly correlated with higher expressions of both MDR and CYP3A two prototypical PXR target genes; nevertheless, this SNP was not associated with PXR expression [26]. Lower mRNA level of CYP3A was reported to be correlated with the variant 1359T > C, a SNP in the promoter region of PXR [27]. In primary human hepatocytes, the C10620T and G10799A variants in the 3′-UTR of PXR are correlated with lower CYP3A activity, and variants 11156C and 11193C could decrease the mRNA level of MDR [25]. The variants G10330A and C10483T of PXR are associated with higher activity of CYP3A [28].

Moreover, PXR SNPs might affect the inducibility of PXR mediated by PXR agonists. It was found that variant R98C fails to transactivate CYP3A4 reporter by a luciferase reporter assay using the CYP3A4 promoter/ enhancer reporter in COS-7 or HepG2 cells when activated by human PXR agonists rifampicin, clotrimazole or paclitaxel [29]. The variants located in the PXR LBD (R98C, Q158K, V140 M, A370T, R381 W and I403v) significantly decreased the up-regulation of CYP3A expression by rifampin compared with wild-type PXR, while variant D136G increases the PXR inducibility activated by rifampin [25, 29–

31]. It is reasonable to speculate that SNPs located in the LBD of PXR could have altered the secondary structure of PXR in this region, which resulted in varied binding affinities for antagonistic ligands such as rifampin. On the other hand, the variants A7635G, C8055T and T1359C located in the intron region of PXR have induced significantly higher expressions of CYP3A after rifampin treatment when compared with the wild-type [25]. A 6-bp deletion in intron 1a (−2,420) of PXR is associated with inactivity of the PXR promoter, which might reduce the inducible ability of PXR to induce its targeted genes [32].

Splice variants of PXR and their functional consequences

A number of alternative PXR splice variants have been identified in human tissues, including PXR.1, PXR.2 and PXR.3 [33, 34]. PXR.1 and PAR.2 are exclusive splice variants in extron 1 of PXR, and PXR.1 is the most common one [34]. PXR.1 encodes a 434-amino acid product and is expressed in both hepatic and extra-hepatic tissues. PXR.2 and PXR.3 come from the deletion of 111 and 123 nucleotides, resulting in the deletion of 37 and 41 amino acids in PXR LBD, respectively [33]. Notably, PXR.2 utilizes a downstream non-AUG codon in translation, which leads to a shorter iso-form and is largely nonresponsive to ligand stimulation [35].

Significant differences have been reported in the baseline level and inducible ability of PXR among different PXR splice variants [7]. The expression level of PXR splicing variants varied among liver samples from 15 Caucasian [36]. Mensah-Osman et al. [37] have observed that the wild-type PXR was not detectable in osteosarcoma cell lines OS187, WOL and COL, and the molecular size of the PXR protein expressed in these osteosarcoma cell lines was different from that of the wild-type PXR. Significant increases have been found for the mRNA levels of UGT1A1 after rifampin treatment when HepG2 cells or Caco-2 cells were transfected with PXR.1 or PAR.2, while no increase was observed for PXR.2 [35]. Compared with PXR.1, PXR.2 could significantly lower the basal level of CYP3A4 and decrease the inducible levels of CYP3A4, CYP2B6 and MDR1 by PXR agonists [29, 38]. By contrast, Tompkins et al. [39] has found that PXR.1 and PXR.2 demonstrated comparable activities in ligand-activated transcriptional up-regulation of CYP3A4. Further studies are needed to reveal the roles of PXR alternative splicing in PXR expression and function.

Role of PXR and its pharmacogenomics in chemotherapeutics metabolism and efficacy

In addition to the well-documented roles of PXR in xeno-biotic metabolism and clearance, as well as its emerging roles in modulating energy metabolism, steroid metabolism, bile acid and bilirubin metabolism, vitamin metabolism, retinoid acid metabolism, bone homeostasis and inflammation, PXR also plays a profound role in cell proliferation, apoptosis, carcinogenesis and cancer treatments [40–49]. Given that cancer patients are typically treated with multidrug regimes, PXR-mediated drug–drug interactions might be even more important in cancer chemo-therapy. Importantly, many drug-metabolizing enzymes and drug transporters participating in the metabolism and clearance of antineoplastic drugs are PXR down-stream target genes [7, 14, 43–49]. Moreover, PXR also regulates the expression of

many genes associated with cell proliferation and apoptosis [22–24, 50]. For instance, PXR agonist rifampicin could significantly increase the mRNA level of fibroblast growth factor (FGF) 19 and stimulate cell proliferation and colon tumor invasiveness [51]. PXR activation could also increase the transcription and protein level of Bcl-2, BAG3, Bcl-XL, BIRC3 and MCL-1 and is negatively correlated with P53, an antitumor gene, leading to enhanced antiapoptosis effect in cancer cells [23, 52–54]. Since fat synthesis and energy metabolism are important in chemical carcinogenesis and chemotherapy of cancer [55], PXR might affect cancer development and chemotherapy by modulating cancer-specific lipid homeostasis [56, 57]. Recently, Xie and colleagues have revealed that PXR sensitized oxidative stress responses in cancerous cells, which might be implicated in increasing chemotherapy efficacy by sensitizing tumors to cellular oxidative damage [58]. In addition, PXR plays an important role in the chemotherapy of hormone-dependent tumor by modulating the steroid metabolic balance [44]. The following drugs are exemplified as chemotherapeutics that are associated with the role of PXR and its pharmacogenomics in cancer treatment (Table 1).

Irinotecan

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin, CPT-11), a water-soluble camp-tothecin analog, is widely used in the treatment for small cell lung cancer, colorectal cancer and several other solid tumors. Being an inactive prodrug, therapeutic effects of irinotecan rely largely on its conversion to an active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) by carboxylesterase in vivo. After bond with DNA topoisomerase, SN-38 inhibits DNA replication, consequently leading to double-strand DNA break and cell apoptosis [59]. Irinotecan can also be metabolized into inactive by-products by CYP3A4 enzyme [60], whereas UGT1A1 represents the key enzyme inactivating the therapeutic SN-38 to yield its β-glucuronide (SN-38G) [61]. In addition, drugs transporters such as *P*-gp (*P*-glycoprotein, encoding MDR1 gene) and canalicular multispecific organic anion transporter (cMOAT) are associated with the efflux of irinotecan and SN-38 out of cancerous cells and decrease intracellular drug accumulation, resulting in drug resistance [62, 63].

An increasing body of evidence suggests that high PXR expression is correlated with decreased efficacy or increased chemo-resistance in irinotecan-based cancer treatment. Raynal et al. [64] have reported that PXR is strongly expressed in colon tumor tissues and displays a great variability of expression. Transfection of the PXR expression plasmid in the colon cancer cell line LS174T desensitized the cancer cells to SN-38; inversely reduced PXR expression by siRNA (small interfering RNA) restored drug sensitivity [64]. In another report, Basseville et al. [65] have found that SN-38 itself functions as a PXR activator and is associated with increased expression of CYP3A4, UGT1A1 and Pgp in both LS180 and HepG2 cells; and over-expression of PXR in LS180 and HCT 116 cells significantly increased their chemo-resistance to SN-38. As such, it is prompted that PXR expression may be regarded as a marker for predicting the chemotherapeutic efficacy of irinotecan and differential expression of PXR might partly account for inter-individual variations in the therapeutic efficacy of irinotecan. When mRNA expression of UGT1A1 elevated with

higher PXR expression, intracellular SN-38G/SN-38 is increased and irinotecan efficacy is decreased [64].

Transgenic mice expressing a constitutively active form of human PXR (VP-hPXR) show significantly higher UGT1A1 activity than wild-type mice, which may lead to increased SN-38 glucuronidation, and decreased efficacy of irinotecan [18]. Gupta et al. [24] have found that rifampicin significantly increases chemoresistance to irinotecan in human ovarian cancerous cell line SKOV-3, and the intra-cellular ratio of SN-38G/SN-38 is higher than that of the control group. Clinical studies demonstrate that rifampicin can reduce the AUC (area under the curve) of irinotecan [66]. SJW (St. John's wort), an over-the-counter remedy for the treatment of depression, is a well-known and potent PXR agonist [67]. In cancer patients, when irinotecan was co-administrated with SJW, the plasma concentrations of SN-38 decreased by approximately 40 % in comparison to irinotecan treatment alone [68]. The expression of PXR downstream target CYP3A, UGT1A1 and P-gP was significantly increased by SJW, leading to accelerated metabolism and efflux of intracellular SN-38 [69]. Given that many drugs are activators of PXR and polypharmacy is often required for cancer treatment, attention should be paid to the drug–drug interactions which might lead to chemotherapeutics resistance by PXR activation. Activation of PXR is also one of the causes for irinotecan self-resistance since SN-38 can activate PXR and up-regulate PXR target genes such as CYP3A4, UGT1A1 and MDR1 [65].

Tamoxifen

Tamoxifen (TAM), a selective estrogen receptor modulator by virtue of competing estrogen receptor with endogenous estrogen, is widely used in the treatment and chemo-prevention of estrogen receptor-positive breast cancer. TAM is converted to a more active 4-hydroxytamoxifen predominantly catalyzed by CYP2D6 and can be further transformed into endoxifen (4-hydroxy-*N*-desmethyltamoxifen) which is equipotent to 4-hydroxytamoxifen [70]. TAM can also be metabolized into lowly reactive *N*-desmethyltamoxifen mainly by CYP3A4 [71]. P-gp could function as the efflux transporter facilitating the excretion of endoxifen from cancer cells and decrease the blood concentrations of endoxifen [72].

Miki et al. [19] have reported that PXR expression in breast cancer cells is positively correlated with Ki-67, a marker of cell proliferation, indicating that PXR possibly plays a pro-proliferative role in breast cancer pathogenesis. The expression of PXR target gene MRP2 (ABCC2) was significantly higher in TAM-resistant MCF-7 cells than that in TAM-sensitive MCF-7 cells; further analysis of revealed that PXR activation was associated with MRP2 over-expression in TAM-resistant MCF-7 cells [73]. In another report, Chen et al. [74] demonstrated that a potent and selective agonist of PXR, SR12813, significantly increased the drug resistance of breast cancer cell lines MCF-7 and MDA-MB-231 to TAM by elevating the expression of CYP3A4 and MDR1, while knockdown of PXR by shRNA (small hairpin RNA) sensitized TAM treatment. OATP 1A2 is a transporter modulating the cellular uptake of estrogen and its metabolites. The expression of mRNA and protein of OATP 1A2 was found to be significantly correlated with PXR expression in human breast cancer tissues [19]. Importantly, PXR agonist rifampin induces OATP1A2 expression and increases the uptake of estrogen, leading to competitive TAM resistance in breast cancer cell

line T47-D, which could be reversed by siRNA of PXR or a specific PXR antagonist A-792611 [75]. In addition, PXR activation might account for TAM self-resistance since TAM and 4-OH-TAM both can activate PXR and increase the expressions of CYP3A4 and MDR1 [76–79], which eventually led to the increased metabolism and efflux of TAM and its active metabolites. On the other hand, PXR activation was also reported to inhibit the proliferation of MCF-7 and ZR-75 breast cancer cells via the up-regulation gene associated with cell cycle arrest, apoptosis such as p21, PUMA and BAX, leaving the net effects of PXR activation in breast cancer treatment rather controversial [50].

Paclitaxel

Paclitaxel, a member of the taxes family, is an important anticancer drug broadly used in the treatment for various malignancies such as breast cancer, ovarian cancer, endometrial cancer and lung cancer. Its mechanism of antitumor is stabilizing microtubules, which leads to defects in mitotic spindle assembly, chromosome segregation, cell cycle arrest, apoptosis and cytotoxicity [80, 81]. Unlike aforementioned irinotecan and tamoxifen, metabolites of paclitaxel are virtually inactive. In humans, Paclitaxel is inactivated by CYP2C8 and CYP3A4 [82, 83]. Inhibition of P-gp in the intestine was associated with significantly lower bioavailability of paclitaxel [84, 85].

PXR activation has been revealed to cause sub-therapeutic responses by enhancing paclitaxel metabolism and promoting the proliferation of cancer cells. Chen et al. [74] have shown that pretreatment with PXR agonist SR12813 increased drug resistance of breast cancer MDA-MB-231 cells to paclitaxel. In human prostate cancer PC-3 cells, activation of PXR by SR12813 up-regulating the expression of CYP3A4 and MDR1, and accelerating paclitaxel metabolism, which resulted in decreased concentration of paclitaxel [86]. PXR expression was also detected in a number of ovarian carcinoma cell lines, in SKOV-3 cells, activation of PXR by rifampin was associated with increased expression of CYP3A4, UGT1A1 but not MDR1 and MRP2, suggesting induction of different PXR target genes is a cell-specific event that could be affected by many cellular factors other than PXR. Notably, activation of PXR induces cell proliferation and paclitaxel resistance in SKOV-3 cells [24]. Furthermore, rifampin accelerates the tumor proliferation in mice carrying SKOV-3 xenografts and promotes SKOV-3 cell proliferation which could be ablated by a PXR antagonist ketoconazole [24].

On the other hand, down-regulation of PXR expression increased paclitaxel efficacy in human prostate carcinoma cell line PC-3 and enhanced apoptosis in human adenocarcinoma cell line HEC-1 [22, 86]. In MDA-MB-231 cells, shRNA-mediated knockdown of PXR significantly compromised the expression of CYP3A4, while sensitized the cells' response to paclitaxel [74].

Moreover, PXR activation also plays a role in paclitaxel self-resistance. As a substrate of CYP3A4 and MDR1, paclitaxel could activate PXR and induce the expressions of these genes. Such auto-induction often leads to drug resistance by increasing the metabolism and elimination of paclitaxel and decreasing the drug concentrations in the target tissues [87–89].

Doxorubicin

Doxorubicin is a nuclear nonselective class I anthracycline antibiotics widely used in the treatment for lymphomas, leukemia, breast cancer and ovarian cancer. Mechanistically, doxorubicin interacts with DNA by intercalation and impairs both DNA and RNA synthesis during tumor cell division [90, 91]. Metabolism of doxorubicin occurs majorly in the liver, where it is converted to doxorubicinol carried out by carbonyl reductases. Both doxorubicin and doxorubicinol could be further transformed as aglycone metabolites via CYP3A enzymes [92]. A number of studies both in vitro and in vivo have established P-gp as a major efflux transporter responsible for excretion of doxorubicin from cells [93].

Both rifampin and the transfection of a VP-PXR plasmid rival cell apoptosis caused by doxorubicin treatment in human colon cancer cell line HCT116 [52]. Harmsen et al. [77] have observed that PXR activation by rifampin increases P-gp activity and reduces the cytotoxic activity of doxorubicin in human colon adenocarcinoma-derived cell line LS180. In contrast, augmented doxorubicin sensitivity in osteosarcoma cells was associated with down-regulation of P-gp by its antagonist ecteinascidin-743, indicating that specific and potent PXR antagonists could be used to increase doxorubicin efficacy [94].

Significant inter-individual and inter-ethnic variations have been observed in the pharmacokinetics and pharmacodynamics of doxorubicin [95]. Such variations could not be explained exclusively by drug–drug interactions. The study by Sandanaraj et al. [95] have shown that doxorubicin clearance and the expression of PXR, CYP3A4 and MDR1 in liver tissues harboring the PXR*1B haplotype are significantly lower than those harboring non-PXR*1B (PXR*1A and PXR*1C) clusters in 62 Asian (Chinese, Malay and Indian) breast cancer patients, indicating that the PXR genotype might be a prognostic factor of patients taking doxorubicin.

Vinblastine

Vinblastine, a vinca alkaloid, is extracted from the Madagascar periwinkle plant Catharanthus roseus [96]. It inhibits cell proliferation during mitosis by binding to the microtubules, which leads to mitotic block and apoptosis. Clinically vinblastine is extensively used in cancer chemo-therapy including acute leukemia, prostate cancer, breast cancer, lymphomas, myeloma, choriocarcinoma and malignant histiocytosis [97, 98]. Vinblastine is mainly metabolized by CYP3A4 and CYP3A5 [99] and transported by ABC (ATP-binding cassette) transporters [100].

Chen et al. [74] have found that PXR knockdown by siRNA increases the therapeutic sensitivity of vinblastine in human breast cancer cell lines MCF-7 and MDA-MB-231. The pretreatment for human prostate cancer cell line PC-3 cell with PXR agonist SR12813 elevates the mRNA level of CYP3A4 and increases vinblastine resistance, which is reversed by PXR knockout, suggesting that PXR is the key regulator in vinblastine resistance [86]. PXR-CYP3A4 might be the potential pathway in vinblastine resistance since PXR activation leads to the up-regulation of CYP3A4 and accelerates vinblastine metabolism, leading to drug resistance.

In addition, vinblastine could activate PXR and elevated the mRNA levels and activities of ABCC2, ABCC3 and CYP3A4 [101, 102], which leads to increased metabolism and efflux of vinblastine, resulted in drug self-resistance.

Other antitumor drugs

ATRA (all-trans retinoic acid) is broadly used in the treatment for APL (acute promyelocytic leukemia), breast cancer, Kaposi's sarcoma and glioma [103]. The antineoplastic role of ATRA is implemented by binding to RARs (retinoic acid receptors) and RXRs to modulate the transcription of a set of genes correlated with cellular differentiation, growth and apoptosis [104–106]. The clinical application of ARTA is restricted by drug resistance [107, 108]. PXR agonist PCN (pregnenolone-16α-carbonitrile), rifampin and dexamethasone are revealed to significantly increase the metabolism and decrease the AUC of ATRA in wild-type mice, but not in PXR-null mice. Further study has found that compared with PXR-null mice, mPXR agonist significantly increases the mRNA levels of mPXR, CYP3A,CYP26, MDR1, ABCC3 and OATP in wild-type mice [109], which might contribute to reduced blood concentrations of ATRA, indicating that PXR antagonists might be hopeful in reversing ARTA resistance.

Cyclophosphamide (CPA) and ifosfamide (IFO), two commonly used DNA alkylating agents in cancer chemo-therapy, are widely used in the treatment for various cancers [110, 111]. They are prodrugs activated via 4-hydroxylation by CYP2B6 and CYP3A4 to generate alkylating nitrogen mustards which could alkylate DNA to form DNA–DNA cross-links, leading to inhibition of DNA synthesis and cell apoptosis [112, 113]. Chang et al. [114] have observed that PXR agonists rifampin and dexamethasone could accelerate the metabolism of CPA and IFO and increase the 4-hydroxylation products in human primary cultures hepatocytes. Meanwhile, the protein expressions of CYP3A4, CYP2C8 and CYP2C9 are induced by the PXR agonists [114], which might accelerate the metabolism of CPA and IFO and be accounted for the enhanced drug efficacy.

Conclusions

To date, chemotherapy continues to be one of the major strategies battling various solid as well as systematic malignances in humans [115, 116]. Although great success has been achieved in this area, inter-individual variability of chemotherapeutic responses has often resulted in drug resistance or unwanted toxicity in clinics [115]. As a promiscuous xenobiotic receptor, PXR plays an important role in chemotherapeutic resistance, drug– drug and gene-drug interactions in cancer treatment [11, 15, 43, 117, 118]. A large number of chemotherapeutic agents are either inducer/inhibitor or substrate of drug-metabolizing enzymes or transporters that can be affected by PXR, leading to inter-individual variability of chemotherapeutic responses in cancer treatment. Therefore, the pharmacogenomics and regulation of PXR hold the promise to be a predict biomarker dictating the prognosis of chemotherapy [19, 22, 64, 65, 73, 74, 86, 109]. Targeted PXR antagonists may potentially improve chemotherapeutics efficacy by inhibiting the metabolism and efflux of anticancer drugs and suppressing the antiapoptosis genes [119]. Nevertheless, comparing to the well-established role of PXR in xenobiotic detoxification, its effects on cancer treatment and

tumor development are yet controversial, and to find out tissue-context aspect of PXR should not be ignored [120]. Direct extrapolation findings from animal studies to human beings are inaccurate and sometimes risky. Thus, clinically targeting PXR as a therapeutic molecule warrants further investigations.

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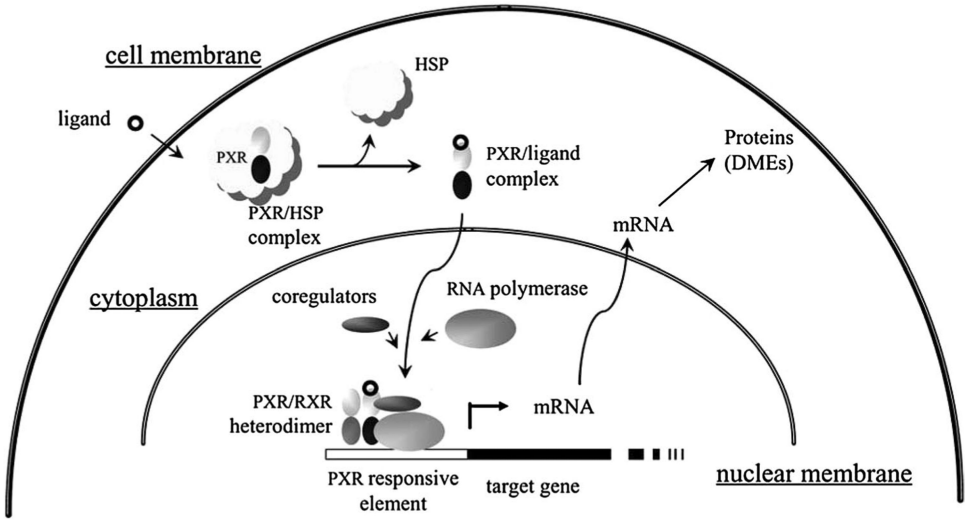

Fig. 1.

PXR regulation of expression of genes for DMEs, transporters and cell process [11]. Upon binding to ligands, PXR dissociates from heat shock protein (HSP), trans-locates into nucleus, forms PXR/RXR heterodimer and stimulates the transcription of target genes, which lead to altered cell functions such as resistance to chemotherapy

Table 1

The function of PXR in the chemotherapy of cancer

Drugs	PXR	PXR target genes	Chemotherapeutic effects	Models	References
Irinotecan	Expression ↑ by transfection	UGT1A1 ↑ UGT1A9 ↑ UGT1A10 ↑ CYP3A4 ↑	Metabolism ↑ Sensitivity ↓	LS174T cells, HCT116 cells	[64, 65]
	Expression ↓ by shRNA and siRNA	UGT1A1 ↓	Metabolism ↓ Sensitivity ↑	LS174T cells, HCT116 cells	[64]
	Activation by rifampicin and SN-38	UGT ↑ CYP3A4 ↑ CYP3A5 ↑ MRP2 ↑ P-gp ↑	Metabohsm ↑ Efflux ↓	Mice, LS180 cells, HePG2 cells, HCT116 cells	[18, 24, 65, 66, 68]
Tamoxifen	Expression ↑ by transfection	Ki-67 ↑ ABCC2 ↑ OATP1A2 ↑	Drug resistance ↑	MCF-7 cells, TAMR-MCF-7 cells	[19, 73]
	Expression ↓ by shRNA		Sensitivity ↑	MDA-MB-231 cells, MCF-7 cells	[74, 75]
	Activation by TAM,4-OH-TAM, SR12813, rifampicin, anandamide and clotrimazole	CYP3A4 ↑ MDR1 ↑ MRP2 ↑ OATP1A2 ↑	Metabolism ↑ Efflux ↑ Drug resistance ↑	MCF-7 cells, T-47D cells, ZR-75-1 cells, MCF-7 cells	[73-79]
		BAX ↑ P21 ↑	Apoptosis ↑	MCF-7 cells, ZR-75-1 cells	[50]
	Inhibition by A-792611	OATPlA2↓	Sensitivity ↑	T47-D cells	[75]
Paclitaxel	Expression↓ by siRNA and shRNA	CYP3A4 ↓ MDR1 ↓	Apoptosis ↑ Proliferation ↓	HEC-1 cells, MDA-MB-231 cells	[22, 74, 86]
	Activation by paclitaxel, SR12813, rifampicin	CYP3A ↑ CYP2B6 ↑ CYP2C8 ↑ MDR1 ↑	Metabolism ↑ Efflux ↑ Apoptosis ↓ Proliferation ↑	HEC-1 cells, PC-3 cells, MDA-MB-231 cells, SKOV-3 cells	[24, 74, 86-89]
Doxorubicin	Avtivation by rifampicin and VP-PXR	BAG3 ↓ BIRC2 ↓ MCL-1 ↓ BAK1 ↓ TP53/p53 ↓ P-gp ↑	Apoptosis ↓ Sensitivity ↓	HCT116 cells, LS180 cells	[52, 77]
	Inhibition by ecteinascidin-743	P-gP↓	Sensitivity ↑	Osteosarcoma cells	[94]
	PXR polymorphisms	Patients harboring PXR*1B showed higher CYP3A4 levels compared with PXR*lA and PXR*lC	Patients harboring PXR*1B showed higher drug clearance compared with PXR*lA and PXR*lC	Patients	[95]
Vinblastine	Activation by SR12813 and vinblastine	ABCC2 ↑ ABCC3 ↑ CYP3A4 ↑	Sensitivity ↓	PC-3 cells, LS174T cells, Patients	[86, 101, 102]
	Expression↓ by siRNA	MDR1 ↑ CYP3A4 ↑	Sensitivity ↑	MCF-7 cells, MDA-MB-231 cells	[74]
ATRA	Activation by PCN, Rifampin and dexamethasone	CYP3A ↑ CYP26 ↑ MDR1 ↑ ABCC3 ↑ OATP ↑	AUC ↓ Sensitivity ↓	Mice	[109]
CPA&IFO	Activation by rifampin and dexamethasone	CYP3A4 ↑ CYP2C8 ↑ CYP2C9 ↑	Metabolism ↑ Sensitivity ↑	Primary cultures hepatocytes	[114]