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Review

Nuclear receptors in the multidrug resistance through the regulation of drug-metabolizing enzymes and drug transporters

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ABSTRACT

Chemotherapy is one of the three most common treatment modalities for cancer. However, its efficacy is limited by multidrug resistant cancer cells. Drug metabolizing enzymes (DMEs) and efflux transporters promote the metabolism, elimination, and detoxification of chemotherapeutic agents. Consequently, elevated levels of DMEs and efflux transporters reduce the therapeutic effectiveness of chemotherapeutics and, often, lead to treatment failure. Nuclear receptors, especially pregnane X receptor (PXR, NR1I2) and constitutive androstane activated receptor (CAR, NR1I3), are increasingly recognized for their role in xenobiotic metabolism and clearance as well as their role in the development of multidrug resistance (MDR) during chemotherapy. Promiscuous xenobiotic receptors, including PXR and CAR, govern the inducible expressions of a broad spectrum of target genes that encode phase I DMEs, phase II DMEs, and efflux transporters. Recent studies conducted by a number of groups, including ours, have revealed that PXR and CAR play pivotal roles in the development of MDR in various human carcinomas, including prostate, colon, ovarian, and esophageal squamous cell carcinomas. Accordingly, PXR/CAR expression levels and/or activation statuses may predict prognosis and identify the risk of drug resistance in patients subjected to chemotherapy. Further, PXR/CAR antagonists, when used in combination with existing chemotherapeutics that activate PXR/CAR, are feasible and promising options that could be utilized to overcome or, at least, attenuate MDR in cancer cells.

Contents

Abbreviations: ABC, ATP binding cassette; AF, activation function; AhR, aryl hydrocarbon receptor; AHRE, AhR element; AIP, aryl hydrocarbon receptor-interacting protein; AKRs, aldo–keto reductases; ARE, antioxidant response element; ARNT, aryl hydrocarbon receptor nuclear translocator; BSEP, bile salt export pump; CAR, constitutive androstane receptor; CCRP, cytoplasmic CAR retention protein; CRE, CREB response element; CYP, cytochrome P450; DBD, DNA-binding domain; DEX, dexamethasone; DMEs, drug metabolizing enzymes; DRE, dioxin-responsive element; EPHs, epoxide hydrolases; ER, endoplasmic reticulum; FXR, farnesoid X receptor; FXRE, FXR response element; GR, glucocorticoid receptor; GSTs, glutathione S-transferases; HREs, hormone response elements; HSP90, 90-kDa heat shock protein; IABP, intra-aortic balloon pump; LBD, ligand binding domain; LBP, ligand binding pocket; LXR, liver X receptor; LXRE, LXR response element; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NATs, N-acetyltransferases; NCoR, nuclear receptor corepressor; NLS, nuclear localization sequence; NMO, NAD(P)H:menadione reductase; OATPs, organic anion-transporting polypeptides; OCTs, organic cation transporters; P-gp, P-glycoprotein; PB, phenobarbital; PBP/PPARBP, PPAR-binding protein; PCAF, P300/CBP-associated factor; PCN, pregnenolone 16-alpha carbonitrile; PLTP, phospholipid transfer protein; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator response element; PXR, pregnane X receptor; QR, quinone reductase; RAREs, retinoic acid response elements; RXR, retinoid X receptor; SJW, St. John's Wort; SMRT, silencing mediator for retinoid and thyroid hormone receptor; SRCs, steroid receptor co-activators; SULTs, sulfotransferases; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene; TIF2, transcriptional mediators/intermediary factor 2; TPR, tetratricopeptide repeat; UGTs, UDP-glucuronosyltranferases; XO, xanthine oxidase; XRE, xenobiotic response element.

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1. Introduction

With an annual economic burden of more than $150 billion, cancer is a major public health problem in the United States. Currently, one in four deaths in the United States can be attributed to cancer [1]. Chemotherapy (including hormone ablation therapy with chemical agents) is one of the three most common treatment modalities for cancer, but its efficacy is limited by drug resistant cancer cells [2–5]. Despite how selective the chemotherapeutic or how specific the intended target is, several barriers still lie between chemotherapeutics and their intended activities to kill tumor cells. One such barrier is the delivery of chemotherapeutics, at effective doses, to the tumor mass. After administration, the drug is first distributed, metabolized, and excreted by the human body. Then, after arriving at the tumor site, the chemotherapeutic agent(s) still need to permeate the tumor microenvironment and enter tumor cells. Several possible mechanisms and molecular alterations associated with tumors have been implicated in their resistance to chemotherapy, including hypoxia secondary to poor vascularization in tumors [6], activation of pro-surviving signals such as NF-κB [7,8], overexpression of p-glycoprotein (P-gp) [9–11], presence of "side populations" of cancer stem cells that express active efflux transporters [12,13], and defective apoptotic mechanisms [14–19]. Due to the limited therapeutic windows and steep toxicity curves associated with most chemotherapeutic agents, altered local metabolism and disposition of cancer drugs present challenges to treatment and may account for the variations in drug efficacy, as exemplified by multi-drug resistance (MDR).

Multi-drug resistance, a clinical phenomenon characterized by decreased intracellular drug retention and changed tumor response, is one of the primary factors that limit effective cancer therapy [20]. Much attention has been directed toward the mechanism behind drug resistance and many efforts have been invested to identify therapeutic approaches that mitigate drug resistance. A number of *in vitro* and *in vivo* models have been developed to study the development of MDR and assess the potential clinical application of MDR modulators [8,12]. For instance, the differential induction of ATP binding cassette (ABC) transporters has been associated with MDR in many cancers [21,22]. However, clinical applications have shown limited success, partially because MDR is a complex process and no single drug metabolizing enzyme (DME) [23] or ABC transporter [10] can induce MDR alone. Novel, multi-targeted strategies are needed to overcome the induction of MDR.

Several nuclear receptor families that regulate drug metabolism and disposition are increasingly recognized for their significance in this process, and treatments targeting them promise to open new avenues to alleviate, or even prevent, MDR. Among these nuclear receptors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR) exhibit great flexibility in recognizing structurally diverse compounds, share significant similarities in ligand binding, and cross communicate during the transactional activation of their target gene promoters, which include cytochrome P450s (CYP) (*e.g.* CYP2B6, CYP3A4 and CYP2C9) [24,25] and MDRs (*e.g.* P-gp) [26]. PXR and CAR have been speculated to play important roles in cancer MDR, because of their elevated expressions in breast [27], prostate [28], intestinal [29], colon [30] and endometrial cancers [31] and their roles as master transcription regulators of a broad spectrum of genes that encode phase I DMEs, phase II DMEs and efflux transporters [32–35].

In this review, we will highlight the recent findings regarding xenobiotic receptor regulation of DMEs and drug transporters and provide insight into nuclear receptor associated MDR during chemotherapy. We will first provide a brief background regarding the structural basis and biological functions of xenobiotic receptors. Then, we will focus on recent discoveries that encompass several key transcriptional regulators of xenobiotic enzyme and transporter expression, including PXR, CAR, proliferator-activated receptors (PPARs) and aryl hydrocarbon receptor (AHR). We will also describe the unique structural properties of PXR and CAR that enable them to recognize and accommodate a broad spectrum of xenobiotics and regulate multiple drug metabolism enzymes and transporters. This review will conclude with a discussion of the clinical significance of nuclear receptor activation mediated drug–drug interaction, as well as the potential uses and limitations of nuclear receptor antagonists that circumvent MDR and enhance the efficacy of existing cancer treatments.

2. Drug biotransformation, metabolism, and excretion systems

Accumulation of xenobiotics, including carcinogens, environmental pollutants, and therapeutic drugs, within the body can profoundly affect human health. The ability to clear these chemicals from our bodies is essential to survival, so naturally, mechanisms that metabolize and excrete these xenobiotics have evolved [36]. Xenobiotics metabolism and disposition are mediated by a large number of DMEs and transporters, and consist of four major stages: absorption/permeability, distribution, metabolism, and excretion. DMEs, which include phase I metabolizing enzymes, phase II metabolizing enzymes, and drug transporters, play an essential role in the metabolism, detoxification, and elimination of xenobiotics.

Phases I and II DMEs biotransform lipophilic xenobiotics into water-soluble metabolites that are more readily effluxed from the cell, and subsequently the body, by transporters. Phase I DMEs consist primarily of a number of dehydrogenases, reductases, and oxidases that detoxify xenobiotics by introducing a polar functional group into their target molecules. Among the phase I DMEs, the cytochrome P450s (CYPs; P450s) super family is the most important family of enzymes in the monooxygenation of lipophilic compounds. CYPs attach a reactive hydroxyl group, which can subsequently be utilized by phase II enzymes for further

disposition, onto xenobiotics. These enzymes are found most abundantly in the liver, but their presence has also been observed in various organs including the lung, gastrointestinal tract, and kidney. Inside the cell, CYPs are membrane-bound enzymes that localize primarily to the endoplasmic reticulum (ER), where CYP catalyzed oxidation reactions are essential to cholesterol and sterol biosynthesis [37]. Certain CYPs are also present in other subcellular compartments, including the inner mitochondrial membranes and lysosomes [38]. Currently, 17 distinct families of CYPs have been identified in humans. CYP families 1–4 and 7, with approximately 17 total members, exhibit low substrate specificity and metabolize a diverse set of xenobiotics [39]; hence, they are believed to play crucial roles in both hepatic and extra-hepatic xenobiotic detoxification and elimination [40]. In fact, CYP2B6 and CYP2C enzymes are involved in the metabolism of approximately 25% and 20% of all xenobiotics, respectively [33]; and CYP3A4, alone, can metabolize approximately 50–60% of clinically used drugs [41–43] and is essential to the metabolism of an extensive range of endogenous substrates, including bile acid and steroid hormones.

Subsequently, phase II DMEs conjugate endogenous ligands with electrophilic xenobiotics or their phase I metabolites, primarily through methylation, esteration, acetylation, glucuronidation, sulfation, and glutathione and amino acid conjugation. Phase II products are usually more hydrophilic than their parental compounds and, thereby, are more readily excreted. Phase II xenobiotic-metabolizing enzymes include quinone reductases (QRs), NAD(P)H:menadione reductases (NMOs), methyltransferases, epoxide hydrolases (EPHs), N-acetyltransferases (NATs), glutathione S-transferases (GSTs), UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs) [44]. Among these phase II DMEs, glucuronidation reactions, catalyzed by several UGT isoforms, play a principal role in phase II metabolism [45,46]. Currently, 19 UGT isoforms have been identified in humans and are divided into three subfamilies, UGT1A, UGT2A, and UGT2B [47]. UGTs localize primarily to the ER membrane, where they catalyze the glucuronidation of a substantial array of endogenous substrates and exogenous compounds [45]. To properly coordinate with phase I DMEs, most phase II DMEs are also preferentially expressed in the liver, intestine, and kidney.

It should be noted that xenobiotic biotransformation does not always yield pharmacologically inactive metabolites, and can, instead, produce pharmacologically active, or even toxic, metabolites. For instance, the CYP3A4-mediated N-dechloroethylation of cyclophosphamide, a nitrogen mustard alkylating agent used to treat cancer and autoimmune diseases, produces a neurotoxic metabolite [48].

Ultimately, intracellular levels of both parental xenobiotics and their biotransformed metabolites are determined by membrane transporter proteins (sometimes called phase III enzymes) [49,50]. Drug transporters modulate the absorption or excretion of a variety of structurally unrelated xenobiotics across the cell membrane and are preferentially expressed in several organs (including the liver and intestines) that are, predictably, important to the efflux of xenobiotics and their metabolites. Depending on the source of energy, these transporters can be divided into two classes: ATP binding cassette transporters that utilize the ATP hydrolysis generated energy, and organic cation transporters (OCT) and organic anion-transporting polypeptides (OATP) that utilize proton gradients [51].

The importance of drug transporters in cancer chemotherapy is well recognized. Of the 48 known human ABC transporters, 11 have already been shown to play roles in MDR in cancer cells [52]. Multidrug resistance-associated protein (MRP) and P-glycoprotein (P-gp or MDR1) are perhaps the most notable ABC transporters, since their constitutive or inducible expression has been observed in a variety of human tumors and contributes to chemotherapeutic resistance, a phenomenon frequently referred to as the "MDR phenotype" [53]. For example, MCF-7 cells with higher multidrug resistance related protein 2 (MRP2) expression are more resistant toward tamoxifen [54], and newly invented ATP-binding cassette transporter-inhibiting peptides and heterocyclic or cyclic substituted amino derivatives that inhibit P-gp functions were found to sensitize cancer cells to chemotherapeutics.

In summary, phase I DMEs, phase II DMEs, and drug transporters orchestrate a defensive system that metabolize and eliminate xenobiotics. These DMEs and transporters are crucial to the protection of the human body from xenobiotics; however, dysregulation of their expression in tumor cells can compromise the efficacy of a variety of chemotherapeutics. For instance, the topoisomerase I inhibitor irinotecan (CPT-11) is commonly used to treat patients with metastatic colorectal cancer. Irinotecan does not exert anti-tumor effects *in vivo* until after it is hydrolyzed into its active metabolite, SN38, by carboxylesterases 1 and 2. Afterwards, SN38 is re-inactivated and metabolized into SN38G by UGTs [55,56]. All the while, both irinotecan and its metabolites are subjected to immediate efflux through transporters, including P-gp and MRP2 [57,58]. As such, the prevalence of certain DMEs and drug transporters directly affect the effectiveness of irinotecan, so manipulation of their expressions and activities has become an attractive strategy to circumvent MDR.

Further, phase I and phase II DME mediated drug disposition is frequently accompanied by drug–drug interactions—when one drug affects the pharmacokinetic or pharmacodynamic mechanisms of another, co-administered drug. Drug–drug interactions lead to either synergistic or antagonistic effects on one or both drugs, alter drug response, toxicity, and elimination, or produce new effects that cannot be observed when either drug is administered alone. For instance, the xanthine oxidase (XO) inhibitor allopuriol is often used to treat conditions associated with hyperuricemia, including gout. Allopuriol is also notorious for prolonging the effective durations of drugs that are metabolized by XO. When co-administered with the immunosuppressant mercaptopurine, which is used to treat acute lymphoblastic leukemia and various autoimmune disorders, the drugs can severely suppress bone marrow and induce pancytopenia and death [59].

Altogether, phase I DMEs, phase II DMEs, and drug transporters mediate the metabolism and elimination of various natural xenobiotics and therapeutic agents, sometimes leading drug–drug interactions. Alterations to their expressions or activities can profoundly impact both their ability to protect the human body against environmental xenobiotics and the effectiveness of therapeutic compounds.

3. The nuclear receptor superfamily

Nuclear receptors are important components of mammalian intercellular signaling mechanisms. The mammalian nuclear receptor superfamily comprises of more than 70 distinct members [60] that are divided into two general subclasses, based on their ligand binding requirement. The first subclass is comprised of ligand-dependent nuclear receptors that are regulated by a diverse group of exogenous compounds and endogenous substrates. These receptors include glucocorticoid receptor (GR), estrogen receptor, androgen receptor (AR), and retinoic acid receptor (RAR). The second subclass of nuclear receptors includes the so-called orphan receptors. These receptors share sequence identity with nuclear receptors but their regulatory ligands still have not been identified [61]. Orphan receptors actually account for approximately 60% of known nuclear receptors [61,62]. Several key orphan receptors, including PPARs, liver X receptors (LXRs), aryl hydrocarbon receptor, constitutive androstane receptor and pregnane X receptor, are known to play crucial roles in development,

homeostasis, and diseases [63]. So naturally, orphan receptors have become the focus of intense academic research and industrial targets for the development of novel therapeutic agents.

Most nuclear receptor share characteristic structural features, including a highly conserved DNA-binding domain (DBD), a less conserved ligand binding domain (LBD), and two transactivation domains: activation function 1 (AF-1) and 2 (AF-2) [64]. Characterized by two C4-type zinc fingers, the DBDs of these receptors recognize receptor specific xenobiotic response elements (XREs) or hormone response elements (HREs), and guide the receptors to the promoter regions of specific target genes. Nuclear receptors bind to their response element as monomers, homodimers, or heterodimers with the retinoid X receptor (RXR), such as PXR and CAR [65]. The LBDs of these receptors can be extraordinary flexible in shape and size. Ligand binding at LBDs triggers conformational changes, within the LBD, to accommodate a spectrum of structurally distinct endogenous and xenobiotic ligands, and recruit co-activators and co-regulatory transcription factors, including transcriptional mediators/intermediary factor 2 (TIF2), steroid receptor co-activators (SRCs), and P300/CBP-associated factor (PCAF) [66–69]. The two transactivation domains guide transcription co-regulators to the target gene promoters. Typically, AF-1 domains are ligand-independent and localize to the amino termini, while AF-2 domains are ligand-dependent and localizes to the carboxyl termini [70].

4. Regulation of drug biotransformation and metabolism by xenobiotic receptors

The significance of nuclear receptors in drug metabolism and disposition is evident from their ability to recognize a variety of structurally diverse compounds and their role in the regulation of many important DMEs [22,71]. Expression of these DMEs and transporters, in response to endogenous and exogenous compounds, are subject to both transcriptional and post-transcriptional regulation. A limited number of studies have indicated that short term alterations to DME and transporter activities and cellular localization can be modulated at the post-transcriptional level. Several protein kinases have been shown to drastically alter the functional state of DMEs, mostly CYPs, through phosphorylation and dephosphorylation [72]. Modulation of these DMEs and drug transporters at the transcriptional level, however, is primarily regulated by the nuclear receptor superfamily of transcription factors, together with co-activators and co-repressors [73]. As aforementioned, several different classes of xenobiotics are able to induce the transcription of genes that encode DMEs and transporters by binding directly to nuclear receptors—or alternatively, these nuclear receptors act as metabolic sensors that respond to both endogenous and exogenous chemicals, and thereby integrating the homeostatic biotransformation of endobiotics and xenobiotics. These nuclear receptors can target, either directly or indirectly, different regulatory sequences found in the promoter regions of DME and drug transporter genes.

4.1. Pregnane X receptor

The pregnane X receptor (PXR; NR1I2; also termed as PAR or SXR) is a member of the nuclear receptor superfamily. Full-length PXR cDNAs was cloned by three independent groups in 1998 and was first found to respond to endogenous pregnanes (21-carbon) steroids that gave rise to its name. Ongoing research has, however, revealed that the biology of PXR is more complex than previously thought—PXR serves as a "molecular sentinel" that localizes to both the cytoplasm and nucleus and is able to bind to a wide spectrum of structurally distinct endobiotic substrates and xenobiotic compounds, including food additives, drugs, and environmental pollutants. It has since been shown to coordinate the detoxification of these endobiotics and xenobiotics by modulating the expression of DMEs, including CYP3A, CYP2B6, and various members of the UGTs superfamily [63,74,75], as well as drug efflux transporters, including P-gp and MRP2 [76]. In addition, PXR has been shown to be involved in the regulation of cholesterol homeostasis and bile acid metabolism, and, possibly, in the development of some cancers [77].

4.1.1. Mechanism of PXR activation

It is widely accepted that the induction of nuclear receptor target genes, by endobiotics or xenobiotics, is mediated through direct interactions between the receptors and their putative responsive elements, located in the promoter regions of these genes. PXR was originally believed to be localized to the nucleus, but later studies have revealed that it is also present in the cytoplasm. After ligand binding, PXR translocates to the nucleus to initiate gene transcription [78] (Fig. 1). Similar to other nuclear receptors, PXR homologs from different species are all structurally related, with a conserved N-terminal DBD, a C-terminal LBD, and relatively short hinge region (amino acids 107–141) that separates the DBD and LBD. The DBD of human PXR (amino acids 41–107) contains two zinc fingers and forms a heterodimer with the retinoid X receptor to bind to specific DNA response elements. The PXR DBD contains a bipartite nuclear localization sequence [79] and contacts specific (A/G)G(T/G)TCA sequences in the promoter regions of target genes [71,74,80]. These specific sequences are arranged as direct repeats separated by three- to five-nucleotide spacers (DR3, DR4, or DR5 elements), everted repeats separated by six or eight bases (ER6 or ER8), or inverted repeats with either no spacers or six-based spacers (IR0 or IR6) [71].

Distinct from other nuclear receptors, PXR possesses a flexible and spacious ligand binding pocket (LBP). This unique LBP enables PXR to ably accommodate a structurally diverse array of both endogenous and exogenous hydrophobic compounds [81]. Like other nuclear receptor LBDs, the PXR LBD contains three layers of α-helices arranged in a so-called "α-helical sandwich" that surrounds the receptor's ligand binding pocket [66]. The PXR ligand-binding pocket is large, flexible, and capable of varying between 1280, unbound, to more than 1600 $Å^3$ in volume [66,82–84] when bound to, usually, lipophilic compounds with a limited number of polar groups [85]. Multiple structural studies have revealed that PXR's LBD can be differentially triggered to expand in volume or adopt unique conformational structures that enable it to accommodate a variety of structurally diverse molecules [66,82]. After ligand binding, PXR undergoes conformational changes before releasing its co-repressor complex and recruits various co-activators, including RXR [65].

Additionally, PXR ortholog sequences vary among species. Although the DBD regions of rabbit, rodent, and human PXRs are conserved and share approximately 95% sequence homology, the LBD are divergent and share only 75–80% amino acid homology. This feature is reflected by pronounced pharmacological divergence in species-specific PXR activation and target gene induction profiles. Accordingly, these species-specific variations compromise the use of animals for PXR ligand screenings.

4.1.2. PXR in DME and efflux transporter regulation

Originally identified as a steroid hormone receptor, PXR mediates the genomic effects of several steroid hormones, including progesterone, pregnenolone, and estrogen, in rodents and humans [74,80]. However, its extreme flexibility in ligand recognition and target gene activation enable it serve as a unique xenobiotic sensor for drug metabolism [66,86,87]. There are a number of studies that have characterized endogenous and exogenous PXR agonists [86,88]. To date, PXR has been observed

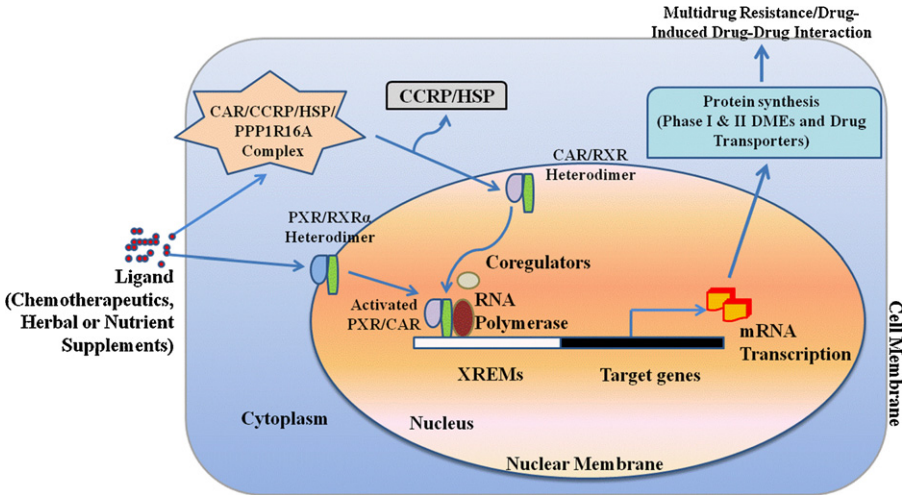

Fig. 1. Regulation of phases I and II DMEs and drug transporter genes by nuclear receptors PXR and CAR. After ligand binding, cytoplasmic fractions of PXR translocates to the nucleus while CAR dissociates from its complex, comprised of tetratricopeptide repeat (TTR), cytoplasmic CAR retention protein (CCRP), 90-kDa heat shock protein (hsp90) and PPP1R16A, and translocates from the cytoplasm to the nucleus. Subsequently, both PXR and CAR form heterodimers with RXR and bind to their respective response elements to stimulate transcription of phases I and II DMEs and drug transporters.

Table 1
PXR and CAR regulations of DMEs and transporters that are associated with xenobiotic metabolism and transport and its co-expression analysis in human prostate tumors (r, correlation coefficient; NA, not available from the data set examined).

Class	Gene	Receptor	References	Co-expression in human prostate tumor?
Phase I drug metabolism enzymes	CYP1A1	CAR	[26,239]	Yes ($r=0.18$, $p=0.00084$)
	CYP1A2	CAR	[161,239]	Yes ($r=0.12$, $p=0.028$)
	CYP2A4	CAR	[26]	NA
	CYP2A6	PXR	[240,241]	Yes ($r=0.16$, $p=0.0029$)
	CYP2B1/2	CAR/PXR	[242]	NA
	CYP2B6	CAR/PXR	[243]	Not for PXR or CAR
	CYP2B10	PXR/CAR	[151,244]	NA
	CYP2C8	PXR/CAR	[121]	Yes for CAR ($r=0.14$, $p=0.011$) and PXR ($r=0.13$, $p=0.016$)
	CYP2C9	PXR/CAR	[24,120,122]	Yes for PXR ($r=0.12$, $p=0.023$) but not for CAR ($r=0.09$, $p=0.095$)
	CYP2C19	PXR/CAR	[245]	Yes for CAR ($r=0.31$, $p=3.2e{-}08$) and for PXR ($r=0.47$, $p=0$)
	CYP2C29	CAR	[246]	NA
	CYP2C37	CAR	[247]	NA
	CYP3A2	PXR	[248]	NA
	CYP3A4	PXR/CAR	[75]	Yes for PXR ($r=0.24$, $p=8.7e{-}06$) and CAR ($r=0.18$, $p=0.00084$)
	CYP3A7	PXR	[25]	Yes ($r=0.21$, $p=1e{-}04$)
	CYP3A11	PXR/CAR	[26]	NA
	CYP3A23	PXR	[248]	NA
	CYP4F12	PXR	[125]	Yes ($r=0.34$, $p=7e{-}11$)
	CYP7A1	PXR	[124]	Yes ($r=0.16$, $p=0.0024$)
	AKR1C1/2	PXR	[125]	Not
	ALDH1	PXR/CAR	[128]	NA
	AKR1B7	PXR/CAR	[126]	NA
Phase II drug metabolism enzymes	UGT1A1	CAR/PXR	[130,131,249,250]	NA
	UGT1A3	PXR	[134]	NA
	UGT1A6	PXR/CAR	[130,135]	NA
	UGT1A9	PXR/CAR	[135]	NA
	UGT2B1	CAR	[135]	NA
	UGT2B5	PXR	[131]	NA
	GSTA1	PXR	[26,251]	Not
	SULT2A1	PXR/CAR	[141,250]	Yes for PXR ($r=0.13$, $p=0.017$) but not for CAR ($p>0.05$)
	SULT1E1	PXR/CAR	[252]	Not for PXR or CAR
	SULT2A2	PXR/CAR	[26,250]	NA
	SULT1A1	PXR	[253]	Not for PXR or CAR
	SULT1B1	PXR	[253]	Yes ($r=0.33$, $p=1.6e{-}10$)
Drug transporters	MDR1	PXR/CAR	[142,254]	Yes for PXR ($r=0.14$, $p=0.0082$) but not for CAR ($p>0.05$)
	MRP1	CAR	[26,255]	NA
	MRP2	PXR/CAR	[143,256]	NA
	MRP3	PXR/CAR	[226,256]	NA
	MRP4	CAR	[148,257]	NA
	SLCO1A4	PXR	[26,145,258]	NA

to bind to a wide range of structurally distinct chemicals, including anticancer compounds [89–92], herbal components and plant extracts [93–95], cholesterol-lowering statins and SR12813 [96–98], the anti-tuberculoid antibiotic rifampicin [96], HIV protease inhibitors [99], vitamins [100], carotenoids [101,102], endocrine disruptors [103,104], pesticides [105,106], plasticizers [103,104,107,108], and PPAR and other nuclear receptor antagonists [109,110]. In response to the aforementioned xenobiotics, PXR activates the transcription of a series of biologically crucial phase I and II DMEs, as well as drug transporters (Table 1) [111].

4.1.2.1. PXR in phase I DME regulation. Several phase I DMEs are regulated by PXR, including a number of CYPs, carboxylesterases, aldehyde and alcohol dehydrogenases, and enzymes involved in heme production and the P450 reaction cycle [26,84,111]. Particularly, PXR is a predominant regulator of the xenobiotic-responsive expression of CYP3A genes. Accordingly, PXR is highly expressed in human livers and intestines, where CYP3A is abundantly distributed and capable of metabolizing a broad range of structurally diverse xenobiotics [41,42,112,113]. A large number of compounds that induce CYP3A expression are also PXR activators [114]. Analysis of the promoter regions of rodent and human CYP3A genes revealed that PXR regulates the xenobiotics-induced expression of CYP3A by binding directly to either direct repeats of TGAACT half-sites spaced by three base pairs (DR3) or everted or inverted repeats of TGAACT half-sites spaced by six base pairs (ER6 and IR6) [65,80,97,115].

Because of the pronounced variances in PXR LBDs across different species, species-specific PXR activator profiles exist. For example, rifampicin, a potent inducer of CYP3A expression in human and rabbit, but not rodent, liver cells, is also a potent activator of human and rabbit PXR, but not rat or mouse PXR. Conversely, pregnenolone 16-alpha carbonitrile (PCN), a robust inducer of mouse, but not human or rabbit, CYP3A, is also a potent activator of rat PXR, but not human or rabbit PXR [97]. Studies using knockout and transgenic mouse models also show that PCN fails to induce CYP3A expression in PXR-null mice and that humanized mice that carry the human, instead of mouse, PXR ortholog respond to rifampicin. These studies further indicate that PXR-regulated induction of CYP3A gene expression is species-specific [116].

In addition to CYP3A4, rifampicin and phenytoin also induce CYP2B6 expression through human PXR in a dose-dependent manner [117,118]. Other human PXR agonists paclitaxel, SR-12813 and rifampicin are able to induce CYP2C8 and CYP2C9 expression in human primary hepatocytes [119–121]. Additional studies provided evidence that several DR4 and DR5 elements are present within a 3500-base-pair sequence upstream from the CYP2C9 start site [24,122]. Notably though, PXR activation was reported to repress, not activate, CYP7A1 expression in rodent models, which may function as a feedback mechanism to counteract bile acids induced stress responses [123,124].

In addition to CYPs, PXR has been shown to regulate the expression of a number of other phase I DMEs that hydrolyze, reduce, and oxidize xenobiotics. Aldo–keto reductases (AKRs), including various NADPH-dependent oxidoreductases such as aldehyde reductase and aldose reductase, have been reported to be PXR target genes. In humans, both AKR1C1 and AKR1C2 genes contain PXR binding sites [125], and recently, Liu et al. [126] found that PXR recognizes and binds to multiple DR4 sites located in AKR1B7 promoter region. Using mouse models, PCN was observed to induce AKR1B7 expression in wild-type, but not PXR knockout, mice. Evans et al., using transgenic mice that express a constitutively active variant of human PXR (VP-PXR), further identified a plethora of other phase I DME genes that are PXR targets. Constitutively active human hepatic VP-PXR appears to upregulate alcohol dehydrogenase 3A2 (ADH3A2), carboxylesterase 2, and aldehyde dehydrogenase 1A7 (ALDH1A7), and down-regulate hydroxysteroid dehydrogenases (HSDs) and betaine-homocysteine methyltransferase [111]. In agreement with these microarray analyses, xenobiotics were found to induce liver and intestine carboxylesterases in a PXR-dependent manner [127,128].

4.1.2.2. PXR in phase II DME regulation. PXR also regulates the expression of several phase II (conjugation) DMEs that facilitate the excretion of phase I biotransformed xenobiotics. These phase II DMEs include UGTs, GSTs, and SULTs [129]. As mentioned above, UGT catalyzed glucuronidation reactions are essential to the clearance of bilirubin, drugs, and xenobiotics. Currently, a number of UGTs, including UGT1A1, UGT1A3, UGT1A4, UGT1A6 and UGT1A9, have been identified as PXR targets [130–135]. Using cultured HepG2 cells, Sugatani et al. [136] identified several potential PXR binding sites, including a DR-3 element, DR-4 element, and PXR response element (PXRE). *In vivo* experiments confirmed that PCN treatments enhance the transcription and activity of UGT1A1 and UGT1A9 in wild-type, but not PXR-null, mice [131]. And another study, conducted by Xie et al. [130], further showed that UGT1A1 activity is markedly up-regulated in "humanized" PXR transgenic mice.

Glutathione S-transferases catalyze the conjugation of glutathione with electrophilic centers in xenobiotics. GSTs are an essential part of phase II detoxification and important to the development of MDR during chemotherapy [32]. PXR was first reported to be involved in the regulation of GSTs in rats [137]. In this study, high concentrations (μM level) of dexamethasone (DEX) induced GSTA2 gene expression via a PXR-dependent mechanism in primary adult rat hepatocytes. Although no canonical PXR-RXR responsive element can be found in the GST2A promoter, PXR appears to induce GSTA2 expression using a 20-bp region (−700 to −683) region containing the antioxidant response element (ARE) [137]. Using transgenic female mice with constitutively active humanized PXR, Gong et al. [138] found that, in response to mammalian oxidative stress, PXR induces the expression of several GST isoforms in a tissue and sex specific manner.

PXR is also involved in the regulation of sulfotransferase gene expression. The SULT gene family encodes more than 10 distinct enzymes that catalyze the transfer of $-SO_3H$ groups from 3′-phosphoadenosine-5′-phosphosulfate donors to endogenous or exogenous substrates [139]. The sulfate conjugated substrates are more polar and more readily excreted and eliminated than their parental molecules. Among SULTs, hydroxysteroid sulfotransferase (SULT2A1) was the first to be identified as a PXR target [140]. Treatment with DEX significantly increases SULT2A1 mRNA and protein expressions in primary cultured rat, but not human, hepatocytes [140]. Importantly, an IR0 element, found in the proximal promoter of SULT2A1, is speculated to be the PXR binding element [141]. Using animal models, subsequent studies have shown that PXR activation also induces the expression of a number of other SULT family members, including SULT1E1, SULT2A1 and SULT2A2 [139].

4.1.2.3. PXR in efflux transporter regulation. PXR activation has also been reported to regulate several efflux transporters, including ABC drug efflux transporters, multidrug resistance-associated proteins, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) [84,91,99,111,124,142,143].

P-glycoprotein, encoded by the ABCB1 gene, plays an important role in reducing drug absorption in the gut lumen. A DR-4 element, located in the upstream enhancer of the ABCB1 gene, has been identified as a direct PXR binding site and studies from different groups have confirmed that human PXR ligands, including

SR-12813, rifampicin, clotrimazole, nifedipine, and mifepristone, potently promote P-gp expression in human primary hepatocyte and colon cancer cell lines [91,142]. In addition, LS180 cells that express constitutively active PXR (VP-PXR) also express P-gp in the absence of ligands [91].

In addition, a novel ER-8 element has been found in the proximal promoter of ABCC2, the gene that encodes MRP2, and is speculated to provide binding sites for PXR/RXR heterodimers. PXR agonists DEX and PCN induce MRP2 mRNA expression in rodent primary hepatocytes collected from wild-type, but not PXR-null, mice; and mutations to the ER-8 element abolish nuclear receptor responses [143]. Another PXR regulated drug transporter is OATP2. In response to bile salts or xenobiotics exposure, PXR/RXR heterodimers bind to four potential PXR response elements (DR3-1, DR3-2, DR3-3 and DR3-4) located in the 5′- flanking regions of the rat OAPT2 gene [144,145].

Altogether, this apparently ever increasing library of ligands and targets has distinguished PXR as a unique and integral mediator of endo- and xenobiotic metabolism and clearance.

4.2. Constitutive androstane/activated receptor

Initially isolated as an orphan nuclear receptor and named MB67, CAR is predominantly expressed in the liver and maintains only a limited presence in certain extrahepatic tissues in humans [146]. Evident from its name, wild-type CAR does not require ligand binding to become activated. Instead, it readily forms heterodimers with RXR and targets retinoic acid response elements (RAREs) in target gene promoters. Much like PXR, CAR functions as a chemical sensor and regulates a broad range of hepatic and intestinal phase I DMEs (CYP3A4, CYP2Bs and CYP2Cs), phase II DMEs (UGTs and GSTs) [147], and drug transporters (MDR1, MRPs and OATP2) [143,148]. Studies have shown that CAR deficient mice are more susceptible to hydrophobic bile acid and lithocholic acid (LCA) induced hepatotoxicity, but are more resistant to acetaminophen [149,150]. CAR also appears to cross-talk with PXR during xenobiotic response. These receptors recognize similar response elements and share a significant number of target genes [151]. Nevertheless, because CAR can induce target gene expression independent of ligand binding, it regulates xenobiotic metabolism in a way distinct from PXR.

4.2.1. Mechanism of CAR activation

CAR belongs to the same subgroup of the orphan nuclear receptor superfamily as PXR, LXR and farnesoid X receptor (FXR). Distinct from most other nuclear receptors, CAR exhibits strong basal transcriptional activity in the absence of ligands. CAR accumulates in the nucleus and can be constitutively active without xenobiotic stimulation [152]. However, CAR can also be activated via ligand binding. Inactivated CAR is retained in the cytoplasm, where it is attached to a complex comprised of tetratricopeptide repeat (TPR), cytoplasmic CAR retention protein (CCRP), 90-kDa heat shock protein (hsp90), and PPP1R16A (Fig. 1) [153,154]. Both ligand dependent and independent activation releases CAR from its cytoplasmic tethering complex and translocates the receptor into the nucleus, where CAR transactivates CAR-inducible genes. Heterodimerization with RXR triggers an allosteric transformation of the CAR LBD, which allows for ligand accommodation. Hence, CAR activation is a rather complex process and involves the binding of an agonist, recruitment of co-activators, dissociation of co-repressors, translocation to the nucleus, heterodimerization with RXR, binding with DNA before the receptor induces gene expression.

A number of CAR ligands, including androstenol, suppress the transcriptional activity of CAR by recruiting co-repressors instead of co-activators [155]. For example, two endogenous CAR ligands, the androstane metabolites androstanol (5α-androstan-3α-ol) and androstenol (5α-androstan-16-en-3α-ol), trigger the dissociation of CAR from its coactivators and, thereby, inhibit the transactivation of CAR. In this case, the inhibition CAR can be reversed after treatment with CAR inducers [155].

In spite of several common characteristics that human and rodent CAR share, such as nuclear translocation after phenobarbital (PB) treatment and PBREM binding, clear species-specific differences exist between human and rodent CAR. For example, 6-(4-chlorophenyl) imidazo[2,1-b][1,3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl)oxime (CITCO) is a potent human, but not mouse, CAR agonist [156]. Phenobarbital-like inducer, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP), the most potent mouse CAR ligand known, does not activate human or rat CAR [114,157]. Several mouse CAR inhibitors, including CaMK inhibitors, androstenol, and progesterone, do not suppress human CAR activity. In addition, several alternatively spliced human CAR variants, termed CAR2 and CAR3, have been identified [158]. These CAR isoforms are not constitutively active and must be activated via ligand binding. Further, because these CAR isoforms do not exist in rodents, data generated from standard rodent models may not reflect human CAR functions accurately.

4.2.2. CAR in DME and efflux transporter regulation

Many DMEs, most notably the CYPs including CYP3A, CYP2B, CYP2C, and CYP2H, that are regulated by CAR are also co-regulated by PXR (Table 1) [26,159]; nevertheless, CAR is an important nuclear receptor that plays unique roles in xenobiotic and endobiotic metabolism. For example, PB and TCPOBOP treatments do not induce the expression of CYP1A1, CYP1A2, or CYP3A11 in $CAR^{-/-}$ mice [26,147,160,161]. Further studies have identified a cis-element ER8 motif upstream of the CYP1A1 as a CAR-responsive element. This ER8 motif is highly conserved across the CYP1A1 promoters across various species and provides a binding site for CAR/RXRα heterodimer transactivation of both CYP1A1 and CYP1A2 genes in human hepatocytes [162].

UGT1A1 is the first UGT that was identified as a CAR target gene. CAR binds to a distal phenobarbital response enhancer module (gtPBREM) in the UGT1A1 promoter [136]. Several groups have established an essential and unique role of CAR in the regulation of the mammalian sulfation system. The CAR agonists PB and TCPOBOP both induce the expressions of SULT1C1, SULT1E1 and SULT2A1 in wild-type, but not $CAR^{-/-}$ mice [148,163]. And further, SULT1A4 and SULT2A expressions, which are essential to the bile acid detoxification process, were elevated in transgenic mice with constitutively activated CAR (VP-CAR) [164]. A number of key phase II DMEs, including UGTs (UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT1A10 and UGT2B36) and GSTs (GSTA1 and GSTA2), were also found to be regulated by CAR [133,163]. Altogether, these discoveries reinforce the notion that CAR serves as a global phase II DME regulator in both humans and many vertebrates (Table 1).

CAR also regulates a number of drug transporters, including MRP2 [143], MRP3, MRP5 [34] and MDR1. CAR is the key regulator of the metabolism of acetaminophen, a widely used analgesic (pain reliever) and antipyretic (fever reducer). Acetaminophen is hepatotoxic at high doses, and CAR regulates the expressions of many DMEs and drug transporters that both contributes to and alleviates acetaminophen induced hepatotoxicity, including the basolateral drug transporters MRP2, MRP3 and MRP4 that effluxes acetaminophen metabolites from the cell. Interestingly though, $CAR^{-/-}$ mice are more resistant toward acetaminophen induced hepatotoxicity than wild type mice. Acetaminophen itself is not hepatotoxic, but its phase I metabolite is—hepatotoxicity only occurs after cellular glutathione stores are depleted and phase I acetaminophen metabolites cannot be converted into inactive

phase II metabolites. CAR$^{-/-}$ mice lack the xenobiotic sensor that initiates acetaminophen metabolism, so hepatotoxic acetaminophen metabolites do not accumulate [150,165].

Altogether, CAR is an integral xenobiotic sensor that regulates the expressions of a wide spectrum of genes involved in the oxidative and conjugative metabolism and subsequent efflux of xenobiotics and endogenous substrates from cells.

4.3. PPARs

Like PXR and CAR, peroxisome proliferator-activated receptors are nuclear hormone receptors involved in xenobiotic metabolism [166]. So far, three main PPAR families have been isolated: PPARα (NR1C1), PPARβ (also called PPARδ, NUC1, or NR1C2), and PPARγ (NR1C3), which are composed of two members, namely PPARγ1 and PPARγ2. These three families of PPARs have overlapping as well as distinct physiological functions, evident from their tissue- and developmental-specific expression patterns, and common and distinct ligands and target genes.

PPARα is predominantly expressed in the intestine, heart, liver, kidney and brown adipose tissues [167]. PPARβ is preferentially expressed in the small intestine, brain and kidney. PPARγ1 is abundantly expressed in liver, while PPARγ2 is expressed exclusively in adipose tissue for adipocyte differentiation [168]. While inactive PPAR–RXR heterodimers are bound to corepressor complexes, composed of nuclear receptor corepressors and silencing mediators for retinoid and thyroid hormone receptors (SMRTs) [169]. After ligand binding, PPARs undergo conformational changes that facilitate the release of corepressors and subsequent recruitment of transcription coactivators, including mediator complex subunit 1 (MED1), CREB-binding protein (CBP/p300), thyroid hormone receptor-associated protein 220 (TRAP220), PPAR-binding protein (PBP/PPARBP), and various coactivator-associated proteins including PRIP and PRIP-interacting proteins with methyltransferase domain (PIMT/NCoA6IP) and coactivators associated arginine methyltransferase/protein arginine N-methyltransferase 4 (CARM1/PRMT4) [170]. These PPAR complexes then modulate transcription by binding to peroxisome proliferator response elements (PPRE) located in the promoter regions of their target genes.

All three PPAR isoforms are critical to maintaining energy homeostasis. Even though they are all involved in the regulation of lipid metabolism, including adipogenesis [171], each PPAR member plays a distinct role in energy metabolism [172]. Further, PPARs are also involved in other, diverse biological processes such as nitrogen metabolism, cell differentiation and proliferation, inflammation, diabetes and cancer.

PPARs have also been proven to be pivotal in the regulation of phase I DMEs, phase II DMEs and efflux transporters. PPARα has been reported, by several different groups, to transactivate CYP4A gene expression [173–175]. Treatment with the PPARα agonist Wy-14643 led to transactivation of CYP4A1 and CYP4A3 in mouse liver, which cannot be observed in PPARα knockout mice livers [176]. In rabbits, the 5′-flanking sequence adjacent to the DR1 element upstream of the CYP4A6 gene was determined to be the PPARα binding site [177]. Further, several PPREs were found in the promoter regions of CYP4A1 and CYP4A6 genes [178]; however, PPARα failed to transactivate CYP4A expression in primary cultures of human hepatocytes [179]. PPARα is also able to regulate murine CYP8B1 expression [180]. Interestingly, PPARα and its agonists have been reported to repress CYP7A1 activity, by attenuating the transactivation of CYP7A1 through HNF-4 [181]. Moreover, recent application of whole-genome DNA microarrays revealed that PPARs modulate a broad variety of CYP genes in human hepatocytes, including CYP2A, CYP2A6, CYP2C8 and CYP2E [179].

PPARs also modulate the expression of several phase II conjugating enzymes. PPARα/RXR heterodimers can bind to PPREs and control the transcriptional activation of UGTs. PPARα activators, such as diethylhexyl phthalate and ciprofibrate, increase UGT isoenzyme mRNA expression in mice [135]. PPARα and PPARγ regulate UGT1A9 expression and activity, in response to arachidonic and linoleic acid metabolites, in human hepatocytes and macrophages and murine adipocytes by binding to a DR-1 response element located between -719 to −706 bp in the promoter region of UGT1A9 gene [182,183]. Fibrates also induce the expression of the phase II DME SULT2A in a PPARα-dependent manner [184]. In addition, fibrates also activate PPARα and induce UGT2B4 expression in human hepatocytes, a phenomenon that cannot be observed in PPARα-null mice. Treatment with PPARα agonists fenofibric acid and Wy-14643 also leads to UGT2B4 mRNA transactivation in human HepG2 and Huh7 cells [185]. Other phase II conjugating enzymes, such as the GST enzymes GSTA1 and GSTM2 are also regulated by PPARα activators [179,186].

Accumulating studies show that PPARs also regulate the genomic expression of drug transporters. In mice, PPARα promotes MDR2 synthesis [187]. In the presence of their agonists, overexpression of either PPARα or PPARγ upregulate ABCA1 gene expression [188]. PPARγ agonist rosiglitazone promotes BCRP transcription and protein expression in monocyte-derived dendritic cells, while the PPARγ antagonist GW9662 blocks the induction of BCRP expression after rosiglitazone treatment [189].

In summary, the above studies show that PPARs are important regulators of DME and efflux transporter expressions. Clinical use of PPARs antagonists may profoundly affect the metabolism and clearance therapeutic molecules.

4.4. Aryl hydrocarbon receptor

The aryl hydrocarbon receptor, also known as the dioxin receptor, is a member of the bHLH–PAS (basic Helix-Loop-Helix–Per-ARNT-Sim) family of transcriptional regulators. AHR resembles CAR and PXR in several ways, including intracellular localization, ligand binding/activation, nuclear localization and target gene activation [190]. In the absence of ligands, AHR is retained in the cytoplasm, where it is bound to a complex comprised of HSP90 [191], AIP (aryl hydrocarbon receptor-interacting protein), p23 [192], and hepatitis virus X protein-associated protein (XAP-2) [193], also known as ARA9 and AIP. The HSP90 and p23 protect the receptor from proteolysis [194], while XAP2 masks the nuclear localization sequence (NLS) of AHR, and thereby prevents its inappropriate transport into the nucleus [195,196]. After ligand binding, HSP90 is released from the complex and AHR, still inside the complex, undergoes a conformational change that exposes the AHR NLS. The NLS then guide the receptor into the nucleus, where AHR forms a heterodimer with aryl hydrocarbon receptor nuclear translocator (ARNT). Then, the ligand-bound AHR-ARNT heterodimer binds to dioxin-responsive elements (DREs) in the promoter regions of a wide range of genes involved in carcinogen and drug metabolism. AHR is capable of recognizing a broad spectrum of non-aromatic and non-halogenated carcinogens and xenobiotic chemicals, including polycyclic aromatic hydrocarbons, aflatoxin benzo[a]-pyrene, heterocyclic amines, 2,3,7,8-tetrachlorodibenzo-p-dioxin, omeprazole, and 3-methylcholanthrene [197,198].

To date, a number of phase I/II and drug transporters, including CYP1As, CYP1Bs, UGT1As [132,199–202] and ABCG2/BCRP [203], have been identified as AHR targets. Notably, by recognizing similar modules in the distal promoter region of target genes, AHR cross-talks with PXR/CAR to orchestrate xenobiotic detoxification [130,204,205]. Recently, Korzeniewski et al. [206] revealed that AHR is also potentially involved in tumor progression, since it was

highly expressed in hyperplasic breast cancer specimens and correlates with significantly lower survival rates. In conclusion, AHR is involved in drug metabolism and may play an important role in tumor progression.

5. LXR and FXR

Two other nuclear receptors that regulate DMEs and efflux transporters are the liver X receptor and the farnesol X receptor.

To date, two members of LXR family, LXRα and LXRβ, have been identified. LXRα is predominantly expressed in the liver and, to a lesser extent, the kidney, spleen and intestine [207]. LXRβ is expressed in nearly every tissue [208]. After ligand binding, LXR forms a heterodimer with RXR, which recognizes DR-4 motifs, termed "LXR response elements" (LXRE), in the proximal promoter regions of target genes [67]. As a cholesterol sensor, LXR recognizes several cholesterol metabolites, including (24S,25)-epoxy-cholesterol and (24S)-hydroxy-cholesterol [209,210], and regulates cholesterol decomposition into hydrophilic bile acids through cholesterol 7α-hydroxylase (CYP7A) in the liver [211–213]. LXR also regulates the expression of several DMEs in humans, including CYP3A4 and CYP2B6 [214].

FXR is mainly expressed in the liver and intestine. As a bile acid receptor, FXR activation suppresses hepatic bile acid biosynthesis and bile acid transport from the intestinal lumen to the liver. Bile acids, including chenodeoxycholic acid, deoxycholic acid, lithocholic acid and cholic acid, are potent FXR activators. After ligand binding, FXR forms a heterodimer with RXR, which binds to FXR response elements (FXREs) in the xenobiotic responsive enhancer modules (XREMs) of various target genes. FXR has been reported to regulate the expression of CYP7A, intra-aortic balloon pump (IABP), phospholipid transfer protein (PLTP) and bile salt export pump (BSEP, ABCC11) [215–217].

Since both LXR and FXR are primarily responsible for the metabolism and homeostasis of endogenous substrates, such as cholesterol and bile acid, but not for the detoxification of xenobiotics, like chemotherapeutics, we will not expatiate on their activation and functions in this review.

6. Expression of xenobiotic receptors in cancer cells and implications in chemotherapy

6.1. Expression and activities of xenobiotic receptors in cancer cells

NR xenosensors, such as CAR and PXR, are expressed in cancer cells. Studies have shown that the CAR activator CITCO inhibits the proliferation and induces apoptosis of glioma stem cells [218]. Although PXR is mainly expressed in liver and intestinal tissues [75], its expression has been also detected in breast, prostate, and gastrointestinal cancers [28,31,219–221], underscoring its clinical relevance in oncology. In a study conducted by Dotzlaw et al. [221], PXR expression was detected in human breast cancer specimens and in T-47D, MCF-7, T-47D-5, and MDA-MB-231, but not in BT20 or MDA-MB-468, human breast cancer cells. PXR activation in breast cancer cells stimulated the expression of organic anion transporter polypeptide 1A2 (OATP1A2), leading to enhanced estrogen effects [222]. Similar to CAR, PXR activation has been found to inhibit breast cancer cell proliferation [223]. Studies conducted by our lab have determined that the PXR expressed in tumor cells is functional. PXR activation in breast and prostate cancer cells stimulates the expression of CYP3A4 and ABCB1 and increases cancer cell resistance toward chemotherapeutics [28,224]. Using a web-based program (http://ist.genesapiens.org), we conducted an *in silico* analysis of the correlation between PXR/CAR expression and mRNA levels of selective DMEs and transporters in prostate tumor tissues. As shown in Table 1, CYP3A4 mRNA expression is strongly correlated with the expression of PXR and CAR, and ABCB1 mRNA expression is significantly correlated with PXR expression in prostate tumor tissues.

6.2. Activation of xenobiotic nuclear receptors by cancer chemotherapeutics

Furthermore, commonly used chemotherapeutic agents can activate human PXR – underscoring the importance of xenobiotic nuclear receptors, such as PXR, in cancer therapy [90,225,226]. Among the chemotherapeutics, both hydroxylated and non-hydroxylated tamoxifen activate PXR [227] and the anti-mitotic agent paclitaxel activates PXR and enhances P-gp mediated drug clearance [91]. Nevertheless, not all chemotherapeutics are subjected to PXR mediated drug metabolism. The semi-synthetic paclitaxel analog docetaxel is not a potent PXR activator and exhibits significantly longer plasma and intercellular half-lives [90].

6.3. PXR and the expression of ABC efflux transporters in cancer cells

The expression of functional PXR in cancer cells and activation of PXR by chemotherapeutics or other compounds can significantly impact tumor response to chemotherapy [28,224]. Enhanced expression of drug transporters, resulting from PXR activation, increases the severity of drug resistance exhibited by tumor cells. Many cancers acquire resistance to chemotherapeutics principally through MDR. Therapeutic agents that activate PXR may achieve lower clinical effectiveness in patients with high tumor PXR expression, since PXR may alter local concentrations of these anti-neoplastic agents. Therefore, untoward activation of PXR in tumor cells can lead to altered metabolism and disposition of chemotherapeutics within tumor tissues. Decreased concentrations of chemotherapeutics at the tumor site, in turn, substantially impact the intended efficacy of chemotherapy, especially *in vivo*—when the bioavailability of active chemotherapeutics is often a limiting factor.

6.4. Implications of PXR activation in drug–drug interactions during cancer chemotherapy

Another implication of untoward PXR activation is the potential drug–drug interactions involved in cancer therapeutics. Because of their role in the regulation of DMEs and drug transporters, nuclear receptors' role in the drug resistance is of great clinical significance and scientific interest. Cancer patients often take other drugs, such as pain relievers, anti-depressants, anti-emetics, or alternative medicines including herbal supplements, in addition to the drugs that target cancer [228]. In many of these cases, PXR activation by drugs like rifampicin or the St. John's Wort component hyperforin leads to upregulations of DMEs. Rifampicin markedly reduces the serum level of bilirubin by enhancing UGT1A1 and MRP2 expressions [229]. St John's Wort (SJW), a herbal anti-depressant, has been reported to trigger drug–drug interactions with various other drugs [230]. Coadministration of SJW compromises the bioavailability and toxicity of immunosuppressants (cyclosporine) [231] and HIV protease inhibitors (nevirapine) [232]. As shown by Kliewer and colleagues, SJW induced drug–drug interactions are mediated through the transactivation of human PXR and CYP3A4 [93]. Hyperforin, an important component of St. John's Wort, induces upregulations of DMEs including CYP3A, which significantly impairs the anti-neoplastic efficacy, through decreased plasma levels, of irinotecan (CPT-11) [233]. Rifampicin, an important drug used during tuberculosis treatment, is a potent human PXR activator and impairs the efficacy of drugs that are metabolized by CYP3A4 and CYP2B6, including paclitaxel,

Table 2
PXR antagonists.

Compound	Indications/usage	IC50	References
Et-743	Antineoplastic agent	2 nM	[91]
Ketoconazole and its analogues (fluconazole and enilconazol)	Antifungal agent	20 μM	[237,238]
Sulforaphane	Dietary isothiocyanate	12 μM	[259]
Coumestrol	Phytoestrogen	12 μM	[260]
A-792611	HIV protease inhibitor	2 μM	[261]
Polychlorinated biphenyls	Synthetic hydrocarbon compounds	10 μM	[262]
Camptothecin	Antineoplastic agent	0.58 μM	[89]
Ecteinascidin-743 (ET-743)	Antineoplastic agent	3 nM	[91]
Leflunamide	Pyrimidine synthesis inhibitor	6.8 μM	[263]
Itraconazole	Triazole antifungal agent	8.96 μM	[263]
SPB03255	Identified by using ligand-based and structure-based (docking) in silica methods	5–25 μM	[263]

midazolam and tamoxifen [234,235]. Therefore, when designing combination therapy or when patients are provided with dietary supplements, potential activations of drug metabolism and resistance pathways must considered.

7. Summaries and perspective

PXR and other nuclear receptors are increasingly recognized as "master" xenosensors. These nuclear receptors regulate an extensive spectrum of genes involved in the metabolism and disposition of both endobiotics and xenobiotics. PXR and CAR share many response elements and crosstalk extensively during the transactivation of their target genes [236]. These "master" xenobiotic receptors are promiscuous and can be activated by most chemotherapeutic agents. While undergoing treatment, cancer patients, especially those who are given several types of drugs, may experience loss of therapeutic efficacy or severe toxicity if PXR/CAR can become activated by anti-neoplastic agents or by other co-administered drugs. The activity of these nuclear receptors affects the pharmacokinetics, toxicity, and drug–drug interactions of many xenobiotic substances including chemotherapeutics.

Therapeutic agents that do not activate PXR/CAR may be preferentially adopted to circumvent the nuclear receptors that are involved drug resistance. Chemical structures can also be modified to prevent these drugs from acting as nuclear receptor ligands. For example, while paclitaxel is potent PXR activator and induces P-gp-mediated drug clearance, its semi-synthetic derivative docetaxel is a poor PXR activator and exhibits enhanced intracellular half-life and efficacy [91]. Targeted therapies that consider PXR or CAR activities/function should be pursued to avoid MDR or re-sensitize patients toward therapeutic agents.

Alternatively, ligands (agonists or antagonists) that modulate nuclear receptor activities have promising therapeutic application. Currently, a growing number of PXR antagonists have been characterized. Enilconazole, ketoconazole, enilconazole, HIV protease inhibitor A-792611, coumestrol and sulforaphane have all been demonstrated to inhibit PXR activation (Table 2) [237,238]. Suppression of PXR or CAR prior to chemotherapy may ameliorate drug resistance in patients that exhibit severe nuclear receptors mediated drug metabolism. Further, studies that identify PXR antagonists are urgently needed, since these antagonists can potentially prevent PXR induced drug–drug interactions. PXR antagonists should, however, be used with caution. PXR plays conserved roles in the metabolism of endobiotics, including bile acids and steroid hormones, and long-term inhibition of PXR or CAR may also cause hypersensitivity to xenobiotics and other toxins. Therefore, development of tissue-specific PXR antagonists will provide the option to selectively disrupt PXR-mediated drug disposition in specific tissues or organs. Alternatively, chemotherapeutics that also do not activate PXR or other xenosensors can also circumvent MDR and ensure treatment efficacy.

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