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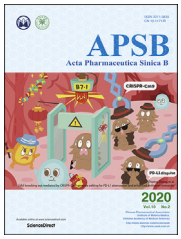

REVIEW

PXR: a center of transcriptional regulation in cancer

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Abstract Pregnane X receptor (PXR, NR1I2) is a prototypical member of the nuclear receptor superfamily. PXR can be activated by both endobiotics and xenobiotics. As a key xenobiotic receptor, the cellular function of PXR is mostly exerted by its binding to the regulatory gene sequences in a ligand-dependent manner. Classical downstream target genes of PXR participate in xenobiotic responses, such as detoxification, metabolism and inflammation. Emerging evidence also implicates PXR signaling in the processes of apoptosis, cell cycle arrest, proliferation, angiogenesis and oxidative stress, which are closely related to cancer. Here, we discussed, in addition to the characterization of PXR *per se*, the biological function and regulatory mechanism of PXR signaling in cancer, and its potential for the targeted prevention and therapeutics.

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1. Introduction

NR1I2 (nuclear receptor subfamily 1 group I member 2) was discovered in 1998 and named as PXR (pregnane X receptor) or PAR (the receptor activated by pregnane) based on its activation by endogenous pregnanes 21-carbon steroids. Besides, human PXR is known as SXR (steroid and xenobiotic receptor)[1,2]. PXR is enriched in small intestine, duodenum, liver, rectum, colon and gallbladder, while its expression in other organs/tissues is either low or undetectable[3] (Fig. 1). This specific distribution of PXR in the enterohepatic system renders its crucial role as a sensor for environmental cues and inducer of xenobiotic response[2].

PXR can be activated by both endobiotic and xenobiotic chemical compounds. Besides pregnane, steroid, bile acids and other endobiotic chemicals, various clinical drugs and environmental pollutants have been demonstrated to activate PXR[1,4–6]. Activated PXR, through direct binding to the genomic regions or indirect crosstalk with other transcriptional factors, controls many genes involved in biotransformation, transport, inflammation, cell cycle arrest, apoptosis and oxidative stress. Many of these biological signaling pathways are closely related to tumorigenesis, indicating an essential function of PXR in cancer development and progression. Indeed, PXR manifests its potential in prevention and treatment for cancers developed from toxic exposure[7,8], virus infection[9], and recurrent inflammation[10]. In this review, we summarized the current understanding of the biological function and regulatory mechanism of PXR in the context of cancer.

2. Gene and protein of PXR

Human *PXR* gene locates in cytoband q13.33 of chromosome 3 with 38507 SNPs (single nucleotide polymorphisms), 2394 deletions, 1403 insertions, 18 substitutions, 8 indels, 4 genetic markers, 17 sequence alterations, 32 tandem repeats and 788 somatic sequence alterations, some of which cause monstrous change of structure and functions of PXR protein[11–13].

PXR protein, approximately 50 kDa, consists of the N-terminal ligand-independent activation function 1 (AF-1), the DNA binding domain (DBD), the relatively short hinge region, and the ligand binding domain (LBD) which contains the ligand-dependent activation function 2 domain (AF-2)[14] (Fig. 2). With the unique flexible large conformation in LBD, the capacity of binding and

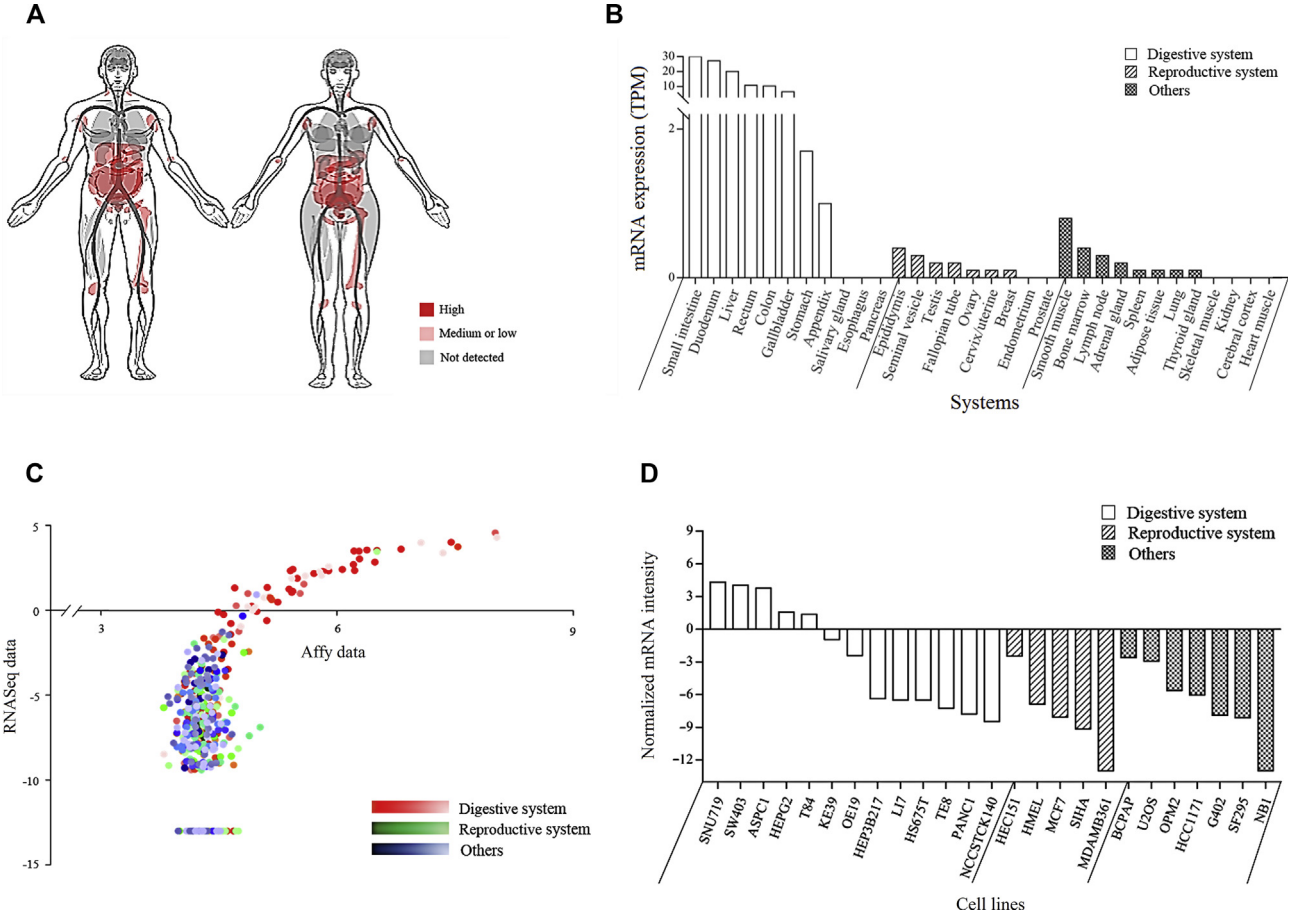

Figure 1 The distribution patterns of PXR. (A) The global expression profiles of PXR in human body. High (15−30), medium or low (0−15) and not detected (below cutoff) level of TPM are indicated in red, pink and gray areas respectively[3] (Image available from https://www.ebi.ac.uk/gxa). (B) Transcripts per million (TPM) of PXR in different organs and systems (Data available from v18.proteinatlas.org. https://www.proteinatlas.org/ENSG00000144852-NR1I2/tissue). (C) Expression of *PXR* mRNA detected by microarray and RNAseq in cell lines from different systems. (D) Expression of *PXR* mRNA in some representative cell lines from different systems (Adapted with permission from https://portals.broadinstitute.org/ccle).

Figure 2 Major domains of hPXR protein. Blue: AF-1 domain; red: the DNA binding domain; green: hinge; and yellow: the ligand binding domain (contains AF-2 domain).

recognizing for a wide variety of hydrophobic ligands makes PXR a multifunctional receptor[15]. It is interesting that PXR could form a homodimer unique to other nuclear receptors (NRs) by tryptophan-zipper (Trp-Zip) interaction in LBD domain, while disruption of this homodimer will significantly deprive PXR activity and its recruitment ability for transcriptional coactivator steroid receptor coactivator 1 (SRC1)[16]. The sequence-specific DNA identification by the DBD of PXR is another aspect for regulating the transcriptional activation[1,17]. A sub-region composing 11 sequence-specific amino acid residues called mitotic chromatin binding-determining region (MCBR) within the nuclear localization signal (NLS) mediates the binding of PXR to the DNA[18]. Mechanically, PXR DBD preferentially binds to the DR (direct repeats)-3, DR-4 (the most preferred DNA-binding motif), DR-9, DR-14, DR-19[17] and ER (everted repeats)-6, ER-8[18,19] in the promoter region of the target genes. Genetic alterations within any domain of PXR could lead to the change of its function. For example, some splicing variants have been reported to have functional deficiency or emulative suppression due to the alteration of encoded amino acid sequences[20,21]. Furthermore, other alternatively spliced isoforms of PXR, whose biological function has not been fully understood, might have some unanticipated roles.

3. The regulatory mechanism of PXR activity

Along with the characterization of the transcriptional activity, the multidimensional regulatory mechanism of PXR has been revealed, including the genetic and epigenetic regulation for PXR expression, transcriptional regulation, subcellular localization, ligand-dependent activation, and protein−protein interaction. The transcriptional activity of PXR also can be modulated through crosstalk with many other NRs, including farnesoid X receptor (FXR)[22], constitutive androstane receptor (CAR)[23−26], peroxisome proliferator-activated receptor α (PPARα)[27], liver X receptor (LXR)[19,28], and androgen receptor (AR)[29] (Fig. 3).

3.1. *Epigenetic regulation for PXR*

The role of epigenetic modulation for PXR transcripts has been defined. Recently, microRNA (miR)-34a, miR-140-3p, miR-148a and miR-449a were found to downregulate the expression of PXR through the identification and interaction at the 3′-untranslated region (3′-UTR) of *PXR* mRNA in the hepatocellular carcinoma cell lines, which might augment the sensitivity of anti-cancer medicines[30−32]. However, among Chinese Han population, no correlation between miR-148a and the expression of PXR or cytochrome P450 3A4 (CYP3A4) was found in livers[33]. Altered 3′-UTR derived from several SNPs of PXR, including rs3732360, rs1054190 and rs1054191, could change the original binding with miR-500a-3p, miR-532-3p and miR-374a-3p[34]. This observation reflected how confound influence the epigenetic modulation and inter-individual variability may have on the activity of PXR. In addition to our limited understanding about miRNA-mediated silence of PXR, recently, PXR activation-mediated regulation for long non-coding RNA (lncRNA) has been shown in xenobiotic metabolism[35] for the first time, indicating that it remains an open field regarding the role of non-coding RNAs (ncRNAs) for PXR activity.

Moreover, within the upstream promoter of PXR transcripts, methylation is a critical modification responsible for reduction of the expression of variant PXR isoforms[21,36], while demethylation agents, such as 5-aza-2-deoxycytidine, could serve as an inducer to increase the expression of PXR isoforms[21], which might be associated with biology and therapeutic outcomes of hepatocellular carcinoma (HCC)[21,36]. Recently, some transcription factors have been shown to regulate PXR abundance as well. For example, transcription factor E26 transformation specific sequence 1 (ETS-1)[37] and *N*-α-acetyltransferase 10 (NAA10)[38], could interact with PXR promoter, and thus enhance the activation of downstream drug resistance related genes.

3.2. *Post-translational modifications (PTMs) of PXR*

PTMs also play a pivotal role in regulating PXR activity (Table 1[32,39−43]). Phosphorylation[44,45], acetylation[40], SUMOylation[42,43], poly(ADP-ribosyl)ation[39], and ubiquitination[32] mediated by modification enzymes could substantially cause a dynamic change of biological traits, subcellular localization, dimerization, protein stability, co-regulator interaction and degradation patterns of PXR. The activity and bioeffects of PXR are reformed as a consequence of PTMs. Of note, *O*-GlcNAcylation and other PTMs have not been defined hitherto.

Protein kinase A (PKA), protein kinase C (PKC) β, cyclin-dependent kinase 1 (CDK1), CDK2, CDK5, cyclin A/E, casein kinase II (CK2), glycogen synthase kinase 3 (GSK3), mitogen-activated protein kinase kinase 1 (MEK1) pathway[47], and

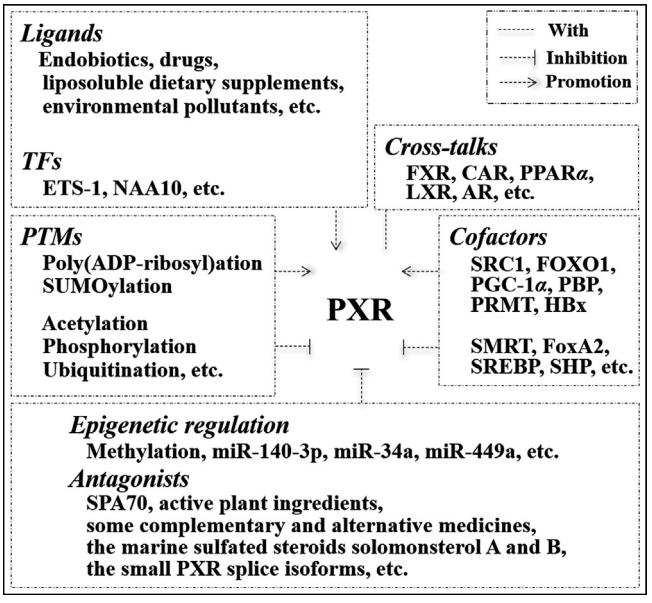

Figure 3 The regulatory mechanism of PXR. Part of regulatory factors for PXR could induce promotion or repression of PXR activity, or crosstalk with PXR by different modes.

Table 1 Post-translational modifications and sites of PXR protein.

PTM	Site
Poly (ADP-ribosyl)ation	LBD[39]
Acetylation	K109[40], K170[41]
SUMOylation	K108, K129, K160, K170[32,42,43]
Phosphorylation[a]	S8, T57, S114, T133, T135, S167, S200, S208, T248, Y249, S256, S274, T290, S305, S350, T408, T422
Ubiquitination[a]	K101

[a]Parts of data[46] are adapted with permission from https://www.phosphosite.org.

70 kDa form of ribosomal protein S6 kinase (S6K) could mediate the phosphorylation of PXR and mostly repress the activity of PXR protein by retaining the PXR protein in cytoplasm, isolating PXR from intranuclear DNA, thus diminishing the transactivation of downstream genes[44,45]. Additionally, PKA activation facilitates the ubiquitination of PXR protein. E3 ubiquitin ligase ring-B-box-coiled-coil protein interacting with protein kinase C-1 (RBCK1) and several others could directly bind and ubiquitinate PXR, resulting in degradation of PXR. Suppressor for gal 1 (SUG1), a subunit of the proteasome, might contribute to the formation of proteolytic fragments of PXR as well. It is noteworthy that the increased level of ubiquitinated PXR was also observed after treatment by MG132 (the inhibitor of 26S proteasome), suggesting PXR is subjected to proteasomal degradation[32].

The E1A binding protein p300 is capable of acetylating PXR at lysine 109 (K109) as the major acetylation site in the hinge, repressing PXR transcriptional activity due to loss of dimerization with RXRα and DNA binding. This modification can be depressed by sirtuin 1 (SIRT1)[40]. Moreover, the lysine acetyltransferase, TIP60, could interact with LBD region of unliganded PXR and acetylate PXR at lysine 170 with a forfeit of ligand-dependent PXR target gene transactivation, which might promote cell migration and adhesion[41]. Recent studies have focused on the involvement of acetylation of PXR in SUMO (small ubiquitin-related modifier)—acetyl switch. On account of acetylation of PXR, SUMOylation of PXR has been stimulated to repress the expression of PXR's target gene[42]. On the contrary, through the interaction with negative charge amino acid-dependent SUMOylation motif (NDSM) in PXR, E2-conjugation enzyme UBCh9-dependent SUMOylation has been demonstrated to activate PXR. It is worth noting that the NDSM-mutated PXR (D115A) is lack of the SUMOylation event[32,43]. Similarly, upon interaction with the C-terminal LBD of PXR, poly (ADP-ribose) polymerase 1 (PARP1) could directly bind and poly (ADP-ribosyl)ate PXR *via* the BRCA1 C terminus (BRCT)/automodification domain (AMD), facilitating the recruitment of PXR to the promotor of target genes and the transactivation of these target genes. Whereas, this positive regulation can be blocked by PARP1 inhibitor 3AB[39].

3.3. *Ligand-dependent activation for PXR*

Recent studies have expanded the profile of upstream activator of PXR, including clinical drugs[48,49], dietary supplements[50], environmental pollutants[7], endobiotics[51] and other chemicals[52]. Unlike many other nuclear receptors, PXR activation can be specie-specific due to the distinction of LBD[53] yet produce similar transcription—regulation profiles due to the conserved DBD[17]. It is worth mentioning that a number of ligands for PXR also could activate other NRs, such as CAR[26] and LXR[19], which impedes the development of PXR targeted therapy, and further complicate their crosstalk. PXR also responds to diverse ligands with different binding modes[54], making it an abstruse target for disease therapy.

Rifampin[48,49,55], Rifaximin[56], St. John's Wort[6], PCN (pregnenolone-16α-carbonitrile)[57] and SR12813[58] are classical agonists for PXR. Recently, a growing number of compounds have been established as PXR activators, basing on their binding capability to LBD and enhancement for the transactivation effect of PXR, such as nontaxane microtubule-stabilizing agents[59], alismanin A[60], the Chinese herbal medicine *Sophora flavescens*[61], U0126[47], PF-06282999[62] and a series of 4-methylenesteroid derivatives isolated from *Theonella* marine sponges[15]. Furthermore, some target genes of PXR, such as sphingomyelin phosphodiesterase acid-like 3A (*SMPDL 3A*)[19], a hepatic nucleotide phosphodiesterase and phosphoramidase involved in purinergic metabolism and anti-inflammatory signaling pathways, is repressed by nonligand-dependent PXR while activated by PXR deficiency or ligand-dependent PXR, which manifests the influence of ligand-dependent activation for PXR on its regulation effects.

3.4. *Antagonist-induced abrogation for PXR*

A large number of antagonists have been reported to inactivate PXR as well, such as some active plant ingredients of sulphoraphane, coumestrol, milk thistle (silybin and isosilybin), valerian and other complementary and alternative medicines (CAM) for cancer[63], the marine sulfated steroids solomonsterols A and B sourced compounds[19–24,64], metformin, ketoconazole, sulforaphane and SPA70[52,58]. Thereinto SPA70[52] is a potent selective antagonist for human PXR, suggesting the PXR targeted therapy may indeed be feasible for drug resistance in cancer. Moreover, *PXR* gene encodes some alternatively spliced isoforms, some of which exert antagonistic functions due to their competitive occupation to activators and absent interaction with target genes[21]. Nevertheless, their influence on disease development remains elusive.

3.5. *Cofactors of PXR*

Several transcription cofactors of PXR have been identified to either enhance or suppress the activity of PXR, depending upon the binding of coactivators' Leu-Xxx-Xxx-Leu-Leu (LXXLL) motifs and corepressors' Ile/Leu-Xxx-Xxx-Ile/Val-Ile motifs to the AF-2 region of PXR[65]. Those co-activators include SRCs[32,44,58], forkhead box O 1 transcription factor (FOXO1), PPAR gamma coactivator 1α (PGC-1α)[44,65], phosphatidylethanolamine binding protein (PBP), and protein arginine methyl transferase (PRMT)[45], while those co-repressors include the silencing mediator for retinoid and thyroid hormone receptors/NR corepressor (SMRT/NCoRs)[45,66], small heterodimer partner (SHP)[47], Sterol regulatory element binding protein 1 (SREBP-1), and forkhead box A 2 transcription factor (FOXA2)[65].

With the intrinsic histone acetyltransferases (HAT) activity, SRC1 could interact with PXR and further recruit secondary coactivators and histone modifying enzymes, such as CBP, p300, coactivator associated arginine methyltransferase 1 (CARM1) and PRMT1, to form a transcriptional complex, allowing the fixation of ligands and expression of target genes. This coactivation can be potentially disrupted by PXR inhibitor—metformin, which is widely used in diabetic patients to improve the metabolism of

glucose and lipids[58,65]. However, there are several reports suggesting that SRC2 but not SRC1 could co-activate PXR activity. In human liver cells, non-phosphorylated serum- and glucocorticoid-regulated kinase 2 (SGK2) has been demonstrated to be involved in PXR mediated co-activation for gluconeogenic genes—phosphoenolpyruvate carboxykinase (*PEPCK*) and glucose-6-phosphatase (*G6Pase*), thereby enhancing gluconeogenesis[65]. Additionally, our previous data has shown hepatitis B virus (HBV) X protein (HBx) could act as a co-factor of PXR in HBV positive HCC[67].

Opposing to the effect of coactivators, SMRTα, abundantly expressed in most human tissues and cancer cell lines, could interact with PXR through the 46-amino acid insert and the C terminal corepressor motif. This interaction is resistant to PXR ligand-induced dissociation and elicits an efficient transcriptional repression for PXR. Another major isoform of SMRT, SMRTτ, also inhibits PXR but with less potency than SMRTα[66]. Previous studies also indicated that SHP is another corepressor for PXR[47]. Nevertheless, this co-regulation of SHP is absent in metformin-mediated suppression for PXR−CYP3A4 pathway[58]. Conversely, PXR has been proposed to attenuate *SHP* promoter activity and to repress *SHP* gene transcription[65], suggesting PXR−SHP interaction might be mutual.

4. Pleiotropic regulation of PXR in cancer

PXR could behave as a node of multiple signaling axes to coordinate disease progressions. The paradigm of PXR action is that, in response to the change of cellular environment, the intranuclear PXR could form heterodimer with retinoid X receptor (RXR) and bind to the specific responsive elements of genes' regulatory domain[68], and then PXR extensively manipulate the expression of downstream genes, including groups of biotransformation enzymes, transport proteins[7,8], inflammatory factors, cell cycle associated proteins and anti-oxidation factors. The expression of the diverse target genes subordinates to the activity of PXR, triggering alteration in detoxification, metabolism, inflammation inhibition, cell apoptosis, cell cycle arrest, proliferation inhibition, tumor migration and anti-oxidative stress. Therefore, PXR and these targets could constitute complex cellular circuits that directly participate in various physiological and pathological progressions (Fig. 4). Due to its extensive biological regulation, the effects of PXR are noted in cancer initiation, promotion and progression, as well as in chemotherapy outcome.

It is generally accepted that cancer, characteristic of multistage progression and diverse etiology, is always diagnosed late and limited in therapy, which highlights the significance of prevention for it. The strategy of prevention based on the pathogenesis of cancer might lie on the intervention of toxic exposure, pathogenic infection, repeating inflammation, immune deficiency, endocrine dyscrasia and other risk factors. Accumulating evidence strongly points to the significant capacity of PXR in detoxification, defense, homeostasis maintaining and proliferation inhibition, which are antagonistic for cancer development. However, PXR and its target genes also have been reported in the association with multidrug resistance and poor chemotherapy outcome in cancer treatment[69], although the mechanism of chemoresistance caused by PXR remains controversial. The pleiotropic effects of PXR in cancer are not completely explicit. It should be emphasized that the location in frontline metabolic organs, the response for internal compound imbalance, and the influence on cellular signal pathways together depict the context-specificity of PXR[70], highlighting PXR might be an intrinsic central target of the huge regulatory network of cancer.

4.1. PXR in metabolism modulation

Activated PXR could mediate xenobiotic detoxification, inhibit hepatic steatosis, and maintain the homeostasis of endobiotic chemicals (such as heme, bilirubin, thyroxin, bile acids, bilirubin, vitamin D, glucose and lipid)[15,65], some nutrients and steroid hormones by promoting biotransformation and elimination of endobiotics and xenobiotics in normal organs. The effect of PXR on detoxification and homeostasis is exemplified by the expression of its target genes, including *CYP*s[7,62], carboxylesterases[8,71], *PEPCK*, *G6Pase*, estrogen sulfotransferase 1E1 (*SULT1E1*)[65], glutathione S-transferases (*GST*s), glutathione peroxidase (*GPx*)[72], ATP-binding cassette family proteins (*ABC*s), organic anion transporting polypeptides (*OATP*s), UDP-glucuronosyltransferases 1A1 (*UGT1A1*)[71], glucose transporter 2 (*GLUT2*)[57] and *MDR*s[73].

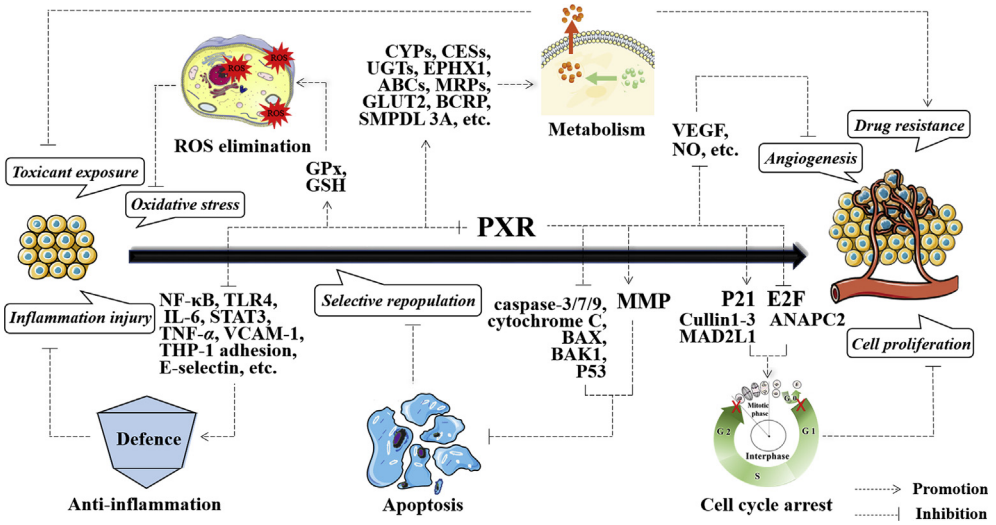

Figure 4 Multifarious target gene-dependent biological effects of PXR. PXR and its target genes constitute complex cellular circuits to participate in cancer-related physiological and pathological progressions.

Hydrolytic biotransformation and excretion by such enzymes and transport proteins[53,57,62] increase water-solubility and elimination of toxic chemicals and reduce the accumulation and toxicity of substrates. Therefore, in the event of the descending expression of PXR and these target genes, detoxification capacity will be impaired[74]. Meanwhile, polymorphisms of PXR's target genes have been documented in cancer. Some of them, such as *ABCG2* rs2231142 variant and rs6857600 minor allele, are associated with a remarkable decrease in risk of chronic lymphocytic leukemia (CLL) and B-cell lymphoma (B-NHL), respectively[8], suggesting polymorphism and bi-direction of these downstream targets might concurrently contribute to PXR's indeterminacy.

Similar to that observed among the elderly, many reports about PXR-mediated transactivation of metabolic enzymes and transport proteins are double-edged for keeping fit in different status. The phase I biotransformation enzyme CYPs, including CYP3A4, CYP3A5, CYP3A7, CYP3A11, CYP2B6, CYP2C9, CYP2C19 and CYP24A1[62,65], are executors of the hydrolytic biotransformation for many therapeutic agents and xenobiotic substance, especially the marker of activated PXR−CYP3A4. CYP3A4 has important implications for the substrate oxidation and pharmacokinetic drug−drug interactions which leads to decreased plasma levels and therapeutic efficacy of anticancer drugs[73]. Therefore, treatment by PXR antagonists, which abolishes *CYP3A4* at the transcriptional level, may facilitate the therapeutic effect[63,64]. However, deficiency of PXR and CYPs might be involved in arsenite[7], di-ethyl-nitrosamine (DEN)[74], some toxic bile acids[51] and other chemicals induced pathological development to cancer. The expression of PXR, *cyp3a* and other PXR's target gene are also found to participate in detoxification for diclofenac (DCF)[75], underlining that effects of intrinsic induction of PXR on target genes always are bidirectional for fitness. In addition to CYPs, the phase I drug metabolizing enzyme (DME) carboxylesterases (CESs)[4], the typical phase II conjugation enzyme UGTs[4], and another detoxification enzyme epoxide hydrolase 1 (EPHX1)[62], might be responsible for the PXR-dependent metabolism of esters, amides, thioesters and/or carbamates, environmental pollutants as well as CYP-mediated oxidations on aromatic/heteroaromatic rings and/or olefinic substituents.

Concurrently, PXR is a shared master orchestrating the expression of transporters[37], which mediate the acceleration of toxicant clearance and decrease of drug effectiveness resulted from "phase 0 metabolism" (reducing the entrance of harmful substances) and "phase III metabolism" (increasing the excretion of their detoxification products)[8]. Through the induction for MDR1, MRP2 (multidrug resistance-associated protein 2), BCRP, UGT1A1 and SULT2A1, PXR generates an export force to remove toxins and drugs, reducing the local cellular accumulation of toxic compounds and giving the individual cell protection against toxic injuries[8,58]. Due to fact that PXR mediates many metabolic enzymes and efflux transporters, the facilitation of drug metabolism and drug−drug interactions appeared inevitable in treatment of anticancer medicines. Upon PXR activation, P-glycoprotein (P-gp, also known as ABCB1 or MDR1)[73], OATP[4,48], MRPs[69,76] and other transporter proteins are upregulated, some of which are correlated with poor prognosis of advanced cancer. Although the PXR signal pathway has drawn increasing interest in recent years for its role in the drug resistance and drug−drug interaction in cancer treatment, the intrinsic expression and activity of PXR can be inordinate given the chaotic nature of most of the cancers. Yet the capacity of xenobiotic clearance might still reflect PXR is a crucial guard in tumor initiation.

Besides the clearance of toxins and drugs, PXR modulates the metabolism of crucial nutritional compounds, such as sugars, amino acids, nucleotides and inorganic ions. This manipulation may impress the development of cancer profoundly. Infinite proliferation and rapid growth of cancer pillage excessive glucose while high acidification from this high glycolytic reaction provides cancer cells with feedback to functional polarization toward a non-inflammatory phenotype, growth and immune evasion of tumor[77]. More remarkably, downregulated expression of two gluconeogenic key enzymes, PEPCK and G6Pase[65], were observed after activation of PXR, which provokes an enigma for the role of PXR in shaping the microenvironment.

The double-edged effect of PXR has also been reported due to its inducibility for toxicant clearance and multidrug resistance. There is evidence showing high-level expression of PXR in stage I and low-level expression in state II and stage III in carcinoma patients. This deficient expression in advanced stages of cancer[67] does not support the harmfulness of PXR activity, suggesting the precise role of PXR deserves further exploration. This inconsistency of PXR might result from its dynamical expression in the different stage of cancer with varying level heterogeneity and disorder. Whilst, false conclusion resulted from indistinguishability between some para-carcinoma tissue and cancer tissue should be noticed as well.

4.2. *PXR in cell cycle arrest*

Other than the regulation for ADME (absorption, distribution, metabolism and elimination) of medicines, toxins, carcinogens and other substance[1], PXR is also capable of suppressing growth, proliferation and migration of cancer cells by inducing cellular cycle arrest. Recently, it has been reported that the antitumor bioregulation induced by PXR impedes the tumor progression, which is achieved *via* functional interaction with the transcriptional regulation of p21 (WAF1/CIP1/CDKN1A), E2F[78,79], cullin1−3, MAD2L1 (mitotic spindle assembly checkpoint protein MAD2A), ANAPC2 (anaphase-promoting complex subunit 2)[79] and other PXR related signaling pathway. In addition, a recent study indicated that PXR could suppress the migration and proliferation of AsPC-1 (human metastatic pancreatic adenocarcinoma) cells, even though its target gene *CYP3A5* is related to acquired drug resistance in PDAC (pancreatic ductal adenocarcinoma)[38], suggesting PXR might play an intricate role in cancer development.

In the intricate regulatory network of cancers, interplay between PXR and cell cycle regulators strikingly enhances cell cycle arrest and prevents the augmentation of cancer development, whereas the lost or greatly diminished expression of PXR might limit this effect in initial cancer[78,79]. Ectopic expressed PXR was found to mediate the promotion of p21(WAF1/CIP1) and the ablation of E2F/Rb, which triggers G0/G1 cell cycle arrest with the inhibition of proliferation and tumorigenicity of colon cancer cells[78]. Consistently, we have shown upon activation of cullin1-3 and MAD2L1, and suppression of ANAPC2 and CDKN1A, rifampicin-activated hPXR could attenuate the growth and proliferation of cervical carcinoma subsequently by mediating G2/M cell cycle arrest[79]. Notably, PXR is involved in hepatic proliferation or inhibit apoptosis to implement liver regeneration as well[2], revealing the context dependent regulatory mechanism. Considering PXR is mainly expressed in colorectum and liver, novel

preventive and therapeutic strategies aimed at preventing or reversing tumorigenesis might have huge potential if the subtle regulation of these PXR associated signaling pathways is achieved in cancer initiation of these tissues.

4.3. PXR in inflammation and injury

PXR-mediated anti-inflammation, anti-oxidative stress[72] and anti-apoptotic responses[51] in the context of cancer[80] have been documented in recent years. Considering the tumorigenic effect of inflammatory injuries and selective repopulation in contributing to the cancer pathogenesis[81], PXR activation may be a promising approach for prevention from injury-induced cancer in preneoplastic stage.

PXR mitigates the inflammation injury generally through the negative regulation of NF-kappa B (NF-κB)[82], Toll-like receptor 4 (TLR4)[80], IL-6, signal transducer and activator of transcription 3 (STAT3), tumor necrosis factor α (TNF-α)[74] and other signaling pathways. Substantial evidence has proved that NF-κB, one of the most central mediator of stimuli-response and immune response, could be observed with increased expression and pro-inflammation in PXR null mice and negatively interact with PXR, triggering the depression for CYP in aggravated small intestinal inflammation[82]. Moreover, a study on increased burden of liver inflammation indicated that IL-6 could restrain PXR activity by inducing differentiated embryonic chondrocyte-expressed gene 1 (DEC1) to competitively bind to the dimerization partner of PXR−RXRα[83]. Homoplastically, heightened severity of necrotizing enterocolitis (NEC) was investigated in the absence of PXR, while the secondary bile acid lithocholic acid (LCA), an agonist for PXR, could activate PXR to negatively regulate TLR4, attenuating NEC in murine intestine, suggesting promotion of PXR-dependent preventive approach might be significant for intestinal inflammation and its subsequent disease[80]. More than an important origin of injure, inflammation induced by cytokines NF-κB, IL-6, STAT3, TNF-α and other many inflammation factors also influences the expression of functional proteins, such as CYP3A11 and glutathione *S*-transferase A2 (GSTa2), which results in DEN-induced hepatic cancer of mice, while based on their negative correlation with PXR, the activation of PXR-related signaling pathway might possess a huge potential for tumorigenesis suppression[74]. Recent studies shed light on PXR activation induced by ginkgolide B, PXR could mediate anti-inflammatory and anti-apoptotic effects on endothelial cells *via* suppressing TNF-α induced THP-1 cells (human acute monocytic leukemia cells) adhesion and expression of vascular adhesion molecule 1 (VCAM-1) and E-selectin and promoting detoxification for staurosporine and doxorubicin[84].

In addition to inflammatory inhibition, PXR activation might blunt the expression of pro-apoptotic genes *TP53* and BCL2 antagonist/killer 1 (*BAK1*) to prevent toxic bile acids-induced apoptosis and subsequent selective repopulation of anti-apoptosis cells in colonic tumorigenesis[51]. Furthermore, after tanshinone IIA treatment, PXR could resist ROS-induced apoptosis and oxidative stress through the inhibition for mitochondrial apoptosis pathway and the regeneration of glutathione (GSH) respectively, which might involve the PXR dependent elevation of mitochondrial membrane potential (MMP), GPx and BCL-2 and the attenuation of caspase-3, caspase-7, caspase-9, cytochrome C and BCL2 associated X (BAX)[72], on this account, alleviating the oxidative injury. It is noticeable, however, genetic or pharmacological activation of PXR−CYP3A4 signaling pathway is involved in ritonavir induced hepatotoxicity[85] and increased sensitization for HS (hemorrhagic shock)-induced hepatic injury[86] in clinical treatment. These discoveries indicated that PXR may be a coordination center for tumorigenesis basing on its transcriptional regulation in inflammation, hepatic injury and homeostasis maintenance.

4.4. PXR in angiogenesis

Along with the pleiotropic effects above, PXR's role in angiogenesis inhibition has been reported in colon cancer as well, and ligand-dependent activation might be required in this progression. Rifaximin, a gut-specific ligand for hPXR[56], could significantly suppress proliferation, migration and expression of PCNA of Caco-2 cells by activating PXR to decrease release of vascular endothelial growth factor (VEGF) and nitric oxide (NO) and phosphorylation of serine/threonine-protein kinase AKT, mTOR and p38 mitogen-activated kinase (p38MAPK), as well as activity of hypoxia-inducible factor 1-α (HIF-1α), p70S6K and NF-κB, while treatment by PXR's antagonist ketoconazole could induce the inhibition for these effects on pro-angiogenic mediators and cancer progression[87]. Furthermore, upon increased survival rate and decreased tumor number, rifaximin treatment also has been shown to perform a chemoprevention for azoxymethane (AOM)/dextran sulfate sodium (DSS)-induced colon cancer dramatically *via* the PXR-dependent response and regulation[88]. Another ligand for PXR−rifampin, a potent angiogenesis inhibitor targeting hepatic cancer developed from hepatitis C virus (HCV)-related liver cirrhosis, could repress human microvascular endothelial cell proliferation and migration *via* downregulating angiogenesis-associated genes[55,89], while whether PXR are involved and its specific mechanism in this progression are waiting for further exploration.

5. Conclusion and prospective

As one of the most crucial gene-regulatory transcription factors, PXR is functioning in a wide range of cellular circuits and biological responses in different organisms. The fact that PXR is responsive to various endobiotic and xenobiotic stimulations makes it a good candidate in mediating carcinogenesis and metabolism of anticancer drugs. The regulatory network weaved by PXR and its upstream and downstream factors has drawn attention in the cancer biology. Indeed, the PXR centric signaling network has been manifested in cancer progression and a growing body of research is adding on to dissect the role of this network in the tumorigenesis. Nevertheless, the specie-specificity of diverse PXR ligands and the influence of PXR signaling on anticancer drug application need to be further defined. Furthermore, PXR targeting prevention and therapy in clinical application are hurdled by the distinctions between the different isoforms with unclear regulatory mechanisms and structurally diverse agonists/antagonists. Note that some PXR variants with antagonistic functions and their potential interaction with other NRs add more to the complexity of PXR targeting cancer treatment. Undoubtedly, the utilization of homeostasis-maintaining nature and the revelation of stage-sensitive bioeffects of PXR indicate a sally port for intervention of cancer development. Better understanding of the regulatory mechanism and biological effects of PXR in different stages of tumor development *via* the advances of research and development and the subduction of toxicity and side effects of antineoplastic will contribute to trailblazing an efficient approach for the prevention and therapy of cancer.

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Author contributions

Yaqi Xing prepared the draft. Jiong Yan edited the manuscript. Yongdong Niu conceived and oversaw the writing of the manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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