Pregnane X Receptor and Cancer: Context-Specificity is Key

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Abstract. Pregnane X receptor (PXR) is an adopted orphan nuclear receptor that is activated by a wide-range of endobiotics and xenobiotics, including chemotherapy drugs. PXR plays a major role in the metabolism and clearance of xenobiotics and endobiotics in liver and intestine via induction of drug-metabolizing enzymes and drug-transporting proteins. However, PXR is expressed in several cancer tissues and the accumulating evidence strongly points to the differential role of PXR in cancer growth and progression as well as in chemotherapy outcome. In cancer cells, besides regulating the gene expression of enzymes and proteins involved in drug metabolism and transport, PXR also regulates other genes involved in proliferation, metastasis, apoptosis, anti-apoptosis, inflammation, and oxidative stress. In this review, we focus on the differential role of PXR in a variety of cancers, including prostate, breast, ovarian, endometrial, and colon. We also discuss the future directions to further understand the differential role of PXR in cancer, and conclude with the need to identify novel selective PXR modulators to target PXR in PXR-expressing cancers.

Keywords: Pregnane X receptor; cancer; MDR; inflammation; nuclear receptor

1. Introduction

The Pregnane X Receptor (PXR), a member of the nuclear receptor subfamily 1, group I (NR1I2), is an orphan nuclear receptor that in humans is encoded by \(NR1I2\) gene. PXR is activated by binding to distinct endobiotics and xenobiotics that are both chemically and structurally diverse [1, 2]. Importantly, as pertinent to this review, these include chemotherapeutic drugs [3–7]. In its apo-form in cells (absence of an agonist), PXR is conventionally associated with transcriptional co-repressors such as nuclear receptor co-repressor I (NCoR1) and NCoR2 [1, 8–10], which mediate repression of PXR basal transcription activity through the recruitment of histone deacetylases [10]. These concepts are contextual, as PXR protein in solution might be associated with co-repressors and co-activators in the presence or absence of ligands, thus challenging the current paradigm [11]. Furthermore, several modifications, particularly post-translational, are not ligand dependent and can modify receptor function \textit{in vitro} and in tissues [12–15, 17]. Nonetheless,
agonists such as rifampicin, SR12813, and chemotherapeutic drugs such as paclitaxel [1, 2, 7, 18] bind to PXR. The consequence of direct binding to the ligand-binding pocket is thought to result in induced conformational changes that lead to dissociation (or a change in functional association with PXR) of co-repressors. There is either concomitant recruitment (or a change in functional association with PXR) of co-activators such as steroid receptor co-activator 1 (SRC-1) and SRC-3 with intrinsic histone acetyl-transferase activity [1, 8–10]. This complex, together, results in chromatin remodeling and subsequent transcriptional activation.

PXR regulates the proliferation of cells; however, again this might be context specific. PXR is important for liver regeneration [19]. PXR activation induces hepatic proliferation and/or inhibits apoptosis through several mechanisms [20–24]. However, PXR activation also induces differentiation of osteoblasts and apoptosis of osteoclasts and certain leukemia cells [25–29], suggesting that control of cell proliferation by PXR is likely tissue and cell-specific. A similar theme plays out in cancer cells, in which, PXR differentially regulates cell growth through multiple mechanisms in a variety of cancers, including liver, prostate, breast, ovarian, endometrial, cervical, and colon [17, 24, 30–39]. Additionally, PXR is involved in regulating metastasis of cancer cells [40–42].

PXR also alters the outcome of chemotherapy in cancers, including breast, prostate, endometrial, ovarian, and colon [30–32, 42–49]. PXR does so by regulating the expression/activity of enzymes and proteins involved in drug metabolism, drug transport, proliferation, apoptosis, anti-apoptosis, inflammation, and oxidative stress. In this review, we will update our prior review [30] with recent developments in PXR as a regulator of tumor development and progression, as well as in chemo-resistance, of major cancer types.

2. Differential Role of PXR in Cancer

2.1. Prostate cancer. In human prostate cancer, PXR is differentially expressed, with higher PXR expression in cancerous versus normal tissues [50, 51]. Human prostate cancer cell lines such as PC-3, LNCaP, and DU145 also express PXR [51]. While activation of PXR in PC3 cells with SR12813, increased mRNA expression of CYP3A4 and MDR1, and resistance of PC-3 cells to paclitaxel and vinblastine, genetic knockdown of PXR increased the sensitivity of PC3 cells to paclitaxel and vinblastine. These results suggested that while activation of PXR confers chemo-resistance, down-regulation of PXR chemo-sensitizes the prostate cancer cells. However, it was also reported that higher PXR expression correlated with good prognosis and increased survival in patients with prostate cancer [50].

Recently, a novel connection between TERE1 tumor suppressor protein and PXR has been identified in Castrate-Resistant Prostate Cancer (CRPC) [52]. TERE1 is a prenyltransferase that synthesizes vitamin K-2, which is a known potent endogenous ligand for the PXR. This study reported that 50% of primary and metastatic prostate cancer specimens exhibited a loss of TERE1 expression. Loss of TERE1 during tumor progression reduces K-2 levels resulting in reduced transcription of PXR target genes involved in cholesterol efflux and steroid catabolism. Thus, a combination of increased synthesis, along with decreased efflux and catabolism likely underlies the CRPC phenotype. LNCaP-C81 cells, which represent a cell model of CPRC, lack TERE1 protein, and displayed decreased expression of the PXR and PXR target genes that control cholesterol efflux and steroid catabolism. However, reconstitution of TERE1 expression in LNCaP-C81 cells reactivated PXR and turned on PXR target genes that coordinate both cholesterol efflux and androgen catabolism. These observations led to the proposition that TERE1 controls the CPRC phenotype by regulating the endogenous levels of Vitamin K-2 and hence the transcriptional control of a set of steroid catabolism genes via the PXR. Other studies corroborate PXR in a similar role in prostate cancer [53–55].

2.2. Breast cancer. The PXR is differentially expressed in human normal or cancerous breast tissue [45, 56–60]. While some studies presented evidence for selective PXR expression in the cancer tissue [57, 58], others have reported PXR expression in both cancerous and adjacent normal tissues [56, 61]. A higher expression of PXR is observed in tumors when compared to adjacent normal tissue [59]. It was also reported that PXR expression was found to be higher in invasive stage than in early phase of breast cancer patients [57]. Along the same lines, PXR expression positively correlated with breast cancer progression [58]. These observations suggest that PXR expression may be context-specific and may play a role in development and progression of breast cancer.

PXR can also induce the proliferation of human breast cancer cells [56–60]. Organic anion-transporting polypeptides (OATPs) is exclusively expressed or overexpressed in breast cancer tissue [57, 59]. In T47-D breast cancer cells, activation of PXR resulted in up-regulation of the expression of OATP1A2 and OATP1A2-mediated estrogen uptake as well as enhanced estrogen-dependent cell proliferation [59]. On the other hand, inhibition or knockdown of PXR resulted in down-regulation of OATP1A2 expression and OATP1A2-regulated estrogen uptake. These observations support a possible role for PXR in breast tumor growth by enhancing the uptake of estrogens via OATPs, consequently increasing levels of intracellular estrogens that activate the estrogen receptor (ER) [59]. It is important to note a significant correlation between PXR expression and ER status in breast cancer. While one study reported higher PXR expression
in ER-positive cases [57], other studies reported an inverse relationship between PXR expression and ER status [56, 58]. Even in the context of this inverse relationship, PXR could contribute to growth in breast cancer cells because of the fact that estrogen binds and activates PXR. While these studies support the role for PXR in inducing breast tumors and show a significant trend supporting the anti-apoptotic role for PXR in breast cancer, a report by Verma et al provided contrary evidence showing that PXR induces apoptosis in breast cancer cells [45].

Besides its role in breast cancer growth and progression, PXR has implications in breast cancer chemo-resistance [56–62]. In MDA-MB-231 and MCF-7 human breast cancer cells, while pharmacologic activation of PXR led to an increased resistance to Taxol as well as an increased expression of CYP3A4 and MDR1 [60], genetic knockdown of PXR sensitized the cells to Taxol, vinblastine or tamoxifen [60]. In MCF-7 cells, it was also shown that paclitaxel induced drug resistance by enhancing the protein expression of PXR and MDR1 [62]. Paclitaxel induction of MDR1 expression and function was significantly diminished in response to knockdown of PXR, suggesting that paclitaxel induces MDR1-mediated drug resistance by activating PXR [62]. Similarly, in MCF-7 and MDA-MB-231 cells, SR12813 treatment not only led to an increased expression of PXR protein as well as drug-resistant genes such as MDR1 and BCRP [61], but also resulted in increased resistance of MDA-MB-231 and MCF-7 cells to docetaxel and 4-hydroxytamoxifen, respectively. Additionally, pretreatment with SR12813 led to reduced apoptosis of MDA-MB-231 and MCF-7 cells induced by docetaxel and 4-hydroxytamoxifen, respectively. Finally, it is interesting to note that higher nuclear PXR expression was positively correlated with the cases that presented resistance to conventional treatments and that metastasized later, suggesting that overexpression of nuclear PXR may be considered as a potential poor prognostic indicator in breast cancer [58]. Although PXR has a differential role in breast cancer, the overall implications of these data support that PXR confers resistance toward chemotherapy in PXR-positive breast cancer.

2.3. Ovarian cancer. PXR is expressed in human ovarian cancer tissues as well as in SKOV-3 and OVCAR-8 human ovarian cancer cell lines [40]. Activation of PXR with rifampicin in SKOV-3 cells not only resulted in induction of CYP3A4 and UGT1A1 expression, but also led to increased proliferation of SKOV-3 cells in vitro and SKOV-3 mouse xenografts in vivo. Furthermore, PXR activation in SKOV-3 cells also conferred resistance to paclitaxel, ixabepilone, and SN-38, indicating that activation of PXR induces both tumor growth and chemo-resistance in ovarian cancer cells. A significant negative relationship between PXR protein status and clinical outcome was also observed in patients with ovarian cancer [63]. Together, these studies support the role of PXR in ovarian tumor progression and chemotherapeutic outcome.

2.4. Endometrial cancer. While PXR expression was not detected in normal tissues, variable levels of PXR expression has been noticed in human endometrial cancer tissues, [64], suggesting that PXR may play a role in endometrial tumor growth and chemo-resistance. Indeed, knockdown of PXR in HEC-1 human endometrial cancer cells decreased the expression of PXR target genes; CYP3A4 and MDR1 as well as enhanced growth inhibition and apoptosis in the presence of paclitaxel and cisplatin [41]. By contrast, overexpression of PXR led to a significant decrease in cell growth inhibition and apoptosis in the presence of paclitaxel and cisplatin [41]. These observations indicate that PXR has implications in endometrial cancer growth and drug response.

2.5. Cervical cancer. PXR is expressed in cervical cancer cell lines such as CaSki and HeLa as well as in cervical cancer tissue samples, although PXR levels were lower in the cancer tissues compared to normal control tissues [39]. Activation of PXR not only resulted in inhibition of proliferation and colony formation of CaSki and HeLa cells by inducing G2/M cell-cycle arrest, but also led to attenuation of CaSki and HeLa xenograft tumor growth in nude mice [39]. PXR-mediated G2/M cell-cycle arrest was accompanied by up-regulation of Cullin1-3 and MAD2L1, and down-regulation of ANAPC2 and CDKN1A. These data support a tumor suppressor role for PXR in cervical cancer as PXR signaling inhibits cervical cancer cell proliferation in vitro and cervical carcinoma growth in vivo.

2.6. Colon/colorectal cancer. There is evidence to support the role of PXR in colon cancer growth and metastasis as well as chemo-resistance. While activation of PXR induced growth, invasion, and migration of LS174T human colon cancer cells and mouse xenografts, knockdown of PXR inhibited proliferation and metastasis to liver from spleen [42]. PXR regulates apoptotic and anti-apoptotic proteins in colon cancer cells similar to the findings observed in hepatocytes [47]. Activation of PXR has been shown to protect HCT116 human colorectal cancer cells and LS180 human colon adenocarcinoma cells from the specific apoptotic insults [46]. The anti-apoptotic effect of PXR associated not only with up-regulation of several anti-apoptotic genes such as BAG3, BIRC2, and MCL-1 but also with down-regulation of pro-apoptotic genes such as BAK1 and P53.

However, it was also reported that PXR expression was lost or reduced in colon tumors, and that PXR overexpression decreased the proliferation of HT29 human colon cancer cells [65]. PXR also inhibited HT29 xenograft tumor growth in mice as a result of cell cycle arrest at G0/G1 phase along with elevated p21 expression and inhibited E2F1 expression. A similar tumor suppressor role for PXR was observed in a very recent study of colon cancer [66]. Treatment
with rifaximin, which selectively activates intestinal PXR, significantly decreased the number of colon tumors induced by azoxymethane (AOM)/dextran sulfate sodium (DSS) in PXR-humanized mice, but not in wild-type or PXR-null mice [66]. Additionally, rifaximin treatment increased the survival rate of PXR-humanized mice compared to wild-type or PXR-null mice. This was accompanied by rifaximin inhibition of up-regulated NF-kB-mediated inflammatory signaling in AOM/DSS-treated PXR-humanized mice. Moreover, rifaximin decreased cell proliferation and increased apoptosis. These results suggest that PXR exhibits a chemopreventive role toward the xenobiotics-induced colon cancer by mediating anti-inflammation, anti-proliferation, and pro-apoptotic events.

Chemotherapy drugs, including PXR activator doxorubicin, induced MDR1 expression in LS180 human colon cancer cells [4]. Activation of PXR with rifampicin decreased intracellular accumulation of doxorubicin and reduced the sensitivity of LS180 cells to the cytotoxic effect of doxorubicin, suggesting that chemotherapy drugs induce chemoresistance by activation of PXR [4]. Along the same lines, tyrosine kinase inhibitors such as Nilotinib and Gefitinib induced MDR1 protein expression and function in LS180 cells [5]. Knockdown of endogenous PXR led to reduced MDR1 induction by Nilotinib and Gefitinib, suggesting that these tyrosine kinase inhibitors induce MDR1 by activating PXR.

Similarly, while activation of overexpressed PXR in LS174T cells induced CYP3A4 expression and increased resistance to irinotecan (CPT-11) and SN38 [67], knockdown of overexpressed PXR reduced CYP3A4 induction and reversed resistance to SN38, suggesting that PXR could alter the outcome of chemotherapy drugs used in the treatment of colorectal cancer. It was also shown in LS180 cells that activation of PXR by SN-38, the active metabolite of irinotecan, resulted in induction of PXR target genes, including CYP3A4, CYP3A5, and MRPI [68]. Consequently, LS180 cells overexpressing PXR were found to be less sensitive to irinotecan treatment, suggesting that the PXR pathway is involved in colon cancer irinotecan resistance [68]. These studies together suggest that PXR inhibition in colon cancer cells can enhance the efficacy of chemotherapy. It was indeed recently shown in HT-29 colon cancer cells that inhibition of PXR with bitter melon extracts resulted in enhanced doxorubicin effect on the cell proliferation, and sensitized the cells to doxorubicin by reducing the expression of PXR target proteins; MDR1, MRP-2, and BCRP [48]. In keeping with colon cancer progression, PXR can activate plasminogen activator inhibitor type I gene expression [69]. More recent data, however, indicates PXR polymorphisms that reduce PXR levels, in colon cancer etiology in the Chinese population [70].

2.7. Hematologic cancers. Recent studies provide a tumor suppressor role for PXR in hematologic cancers. Initially, it was demonstrated that PXR-null mice developed B cell lymphoma in an age-dependent manner, suggesting a tumor suppressor role for PXR in B-1 cells [71]. In chronic myeloid leukemia (CML) patients, it is known that the expression and activity of the uptake transporter human organic cation transporter 1 (hOCT1) positively determines the favorable outcome to Imatinib treatment [28]. Pharmacologic activation of PXR with rifampicin or SR12813 in KCL22 CML cell line and CML primary cells resulted in up-regulation of hOCT1 expression, suggesting that PXR agonists may be potentially used to improve the efficacy of Imatinib in patients with CML [28]. In another study of multiple myeloma, gene expression of uptake carriers, xenobiotic receptors, phase I and II drug metabolizing enzymes, and efflux transporters was examined in multiple myeloma cells of newly-diagnosed patients [29]. The patients with a favorable outcome exhibited an increased expression of xenobiotic receptors and their target genes, influx transporters and phase I/II drug metabolizing enzymes. In contrast, the patients with unfavorable outcome displayed a global down-regulation of xenobiotic receptors and the downstream detoxification genes.

2.8. Other cancers. PXR also has implications in the growth and/or chemoresistance of several other cancers [35, 72–76]. For example, in osteosarcoma cells, PXR activation is associated with chemoresistance [77]. In this context, human PXR transfected normal osteoblast cells (hFOB) show increased proliferation in culture when exposed to Bisphenol A, a human PXR ligand [78]. In Barrett’s esophagus patients, PXR expression is higher in high-grade versus low-grade dysplasia, suggesting that PXR may be involved in tumor progression in Barrett’s esophagus [79]. PXR was suspected to contribute to chemo-resistance in head and neck squamous cell carcinoma [75] but not to survival [80]. Very recently, PXR has been shown to contribute to chemo-resistance in BGC-823 human gastric cancer cells [81] and in the pancreatic ductal adenocarcinoma cells [82]. Finally, PXR has also been shown to play a role in promoting the growth and chemo-resistance of liver tumors [35, 76]. However, PXR over-expression portends a favorable prognosis in pancreatic adenocarcinoma [83] but might aggravate liver tumors [72, 84, 85]. PXR is also more recently implicated as a driver of DNA damage in cutaneous carcinogenesis [86]. Like colon carcinogenesis, a PXR polymorphism in the 3’ UTR predicts for low PXR levels and increased lung cancer risk in smokers from China [87]. Very recently, PXR was proposed to be a novel biomarker for predicting drug resistance in non-small cell lung cancer patients [88].

3. Future Directions

The differential role of PXR in cancer suggests that several mechanisms may be involved in PXR-mediated tumor growth or chemotherapeutic response. Indeed, these may also contrast with cancer risk alleles, in that, PXR expression
would contextually give rise to tumors. Identifying all the mechanisms will be critical to thoroughly understand the role of PXR in tumor progression or suppression as well as in chemo-resistance or chemo-sensitivity. For example, PXR activation induces steatosis [89–93] and many induced lipogenic pathway targets like CD36 are indeed implicated in malignancy [94–96]. Along the same lines, PXR activation promotes diet-induced obesity and type 2 diabetes [97] by deregulating glucose and lipid homeostasis [98–100]. It is now well known that obesity and type 2 diabetes predispose the human patients to cancer. Thus, it is important to understand whether PXR dependent pathways play a role in mediating cancer in obese and type 2 diabetic patients.

Future studies also need to be focused on comprehensively identifying the PXR target genes, including noncoding RNAs, with their oncogenic or tumor suppressor nature in a cell/context-specific manner [17, 82, 101, 102]. It is known that PXR undergoes post-translational modifications such as phosphorylation and acetylation [13–15, 18, 103–106]. In keeping with the same theme, PXR is also regulated at transcriptional and post-transcriptional level [15, 17, 107–114]. It is possible that some of these modifications may contribute to tissue/context specific PXR activity in tumors. A comprehensive investigation of such mechanisms in normal and tumor tissues will be useful to therapeutically target PXR in PXR-expressing cancers.

Several nuclear receptors induce tissue/context-specific phenotype in an isoform/alternative splice variant-dependent manner [30]. The differential effects of PXR in different cancer tissues might be contributed by different isoforms/alternative splice variants of PXR as three PXR isoforms (i.e., PXR.1, PXR.2 and PXR.3) exhibit differential expression, ligand binding affinity, and transcriptional activity [1, 56, 58, 104–118]. Indeed, PXR isoforms, PXR.1 and PXR.2, were found to be differentially expressed in human breast cancer [56, 58]. While low metastatic potential MCF cells expressed PXR.1 but not PXR.2 mRNA [56], high metastatic potential MDA-MB-231 cells expressed higher levels of both PXR.1 and PXR.2 mRNA [56]. Very recently, a novel PXR isoform displaying a dominant negative activity has been identified in human hepatocellular carcinoma patients [119]. This isoform was found to be regulated by DNA methylation, and associated with outcomes of patients with hepatocellular carcinoma treated by resection. Tumor-specific regulation of isoforms or splice variants of some proteins has been reported to have very significant functional consequences [120]. Indeed, the spliced murine PXR, mPXRΔ171−211, exhibits repressive action rather than activation [121]. Identifying isoforms and spliced variants in human tumors and non-tumor tissues would be critical to defining the importance of the isoforms and variants of PXR in human cancer. Isoforms or spliced variants of PXR might favor selective PXR-protein interactions [104, 122].
Table 1: Role of PXR activation in specific cancer types.

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Characteristics of PXR activation (References)</th>
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<tbody>
<tr>
<td>Prostate cancer</td>
<td>Increases tumor progression and resistance to the chemotherapy drugs [51, 52]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Increases cell proliferation [59] and resistance to the chemotherapeutics [60–62]</td>
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<tr>
<td></td>
<td>Inhibits cell proliferation and induces apoptosis [45]</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Induces cell proliferation, tumor growth and resistance to the chemotherapeutics [40]</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Decreases cell growth inhibition and apoptosis induced by the chemotherapy drugs [41]</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Inhibits cell proliferation and tumor growth [39]</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Increases cell growth, invasion and metastasis [42]. PXR activation also increases oxidative stress and anti-apoptotic activity, and decreases pro-apoptotic activity [44, 46]. Moreover, PXR activation enhances resistance to the chemotherapy drugs [4, 5, 48, 67, 68]</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Decreases inflammation, cell proliferation and tumor growth [65, 66].</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Promotes tumor growth and chemo-resistance [35, 76]</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>Contributes to chemo-resistance [81]</td>
</tr>
<tr>
<td>Hematologic cancers</td>
<td>Inhibits development of B cell lymphoma [71] and sensitizes chronic myeloid leukemia cells to the chemotherapeutics [28]</td>
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including PXR-co-regulator interactions. Thus a complete definition of PXR-protein interactions in specific tumor tissues would also be needed to comprehensively understand the effects of PXR activation. For example, in breast cancer, while it has been noted that nuclear localization of PXR portends a poor prognosis [58], another report suggests that PXR expression portends a favorable prognosis [45].

It is also possible that PXR polymorphisms contribute to the differential role of PXR in human cancers. Recent studies showed the interaction of PXR polymorphisms with human diseases, including cancer [123]. While some PXR polymorphisms did not seem to interact with cancer growth, progression, or drug response [124–126], several others were found to be significantly associated with cancer risk, growth, progression, or therapeutic outcome. For instance, the PXR polymorphisms have been shown to be associated with increased lung cancer risk in smokers [87, 127], higher prostate-specific antigen levels in prostate cancer patients [54], lymphoma risk [128], pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in breast cancer patients, pharmacokinetics and toxicity of irinotecan in colorectal cancer patients [129], risk of colorectal cancer [130], Barrett’s esophagus and esophageal adenocarcinoma [131], and docetaxel disposition in nasopharyngeal cancer patients [132]. Hence, a complete mapping of PXR polymorphisms is required to fully understand the PXR activation in a variety of tumors.

4. Conclusion

There are tissue/context specific consequences for PXR expression in cancer and normal tissues [30, 133]. Several mechanisms have been proposed for PXR-mediated effects in cancer and include regulation of the genes involved in drug metabolism, drug transport, cell proliferation, metastasis, apoptosis, anti-apoptosis, inflammation, and anti-inflammation. Indeed, there is a complex interaction between PXR and p53 such that p53 can suppress PXR and drug metabolism and eventually enhance effects of chemotherapy; yet, PXR, when activated inhibits p53 and thus, decreases apoptosis. Therefore, a contextual relevance of these interactions remains at play in any given tumor type [122]. PXR has been proposed as a therapeutic target in treating several human diseases including cancer [30, 134–140]. Depending on the cancer tissue or cellular context, PXR activation or inhibition has been shown to exert anticancer phenotypes. Currently, there are several small molecules [135–137, 141–143] available to either activate or inhibit PXR function in cancer cells. However, there are no selective PXR modulators and identification of such novel selective small molecule modulators of PXR will be beneficial to improve the therapeutic outcomes in PXR-expressing cancers.

Competing Interests

The authors declare that they have no competing interests.

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