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Pregnane xenobiotic receptor in cancer pathogenesis and therapeutic response

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Abstract

Pregnane xenobiotic receptor (PXR) is an orphan nuclear receptor that regulates the metabolism of endobiotics and xenobiotics. PXR is promiscuous and unique in that it is activated by a diverse group of xenochemicals, including therapeutic anticancer drugs and naturally-occurring endocrine disruptors. PXR has been predominantly studied to understand its regulatory role in xenobiotic clearance in liver and intestine via induction of drug metabolizing enzymes and drug transporters. PXR, however, is widely expressed and has functional implications in other normal and malignant tissues, including breast, prostate, ovary, endometrium and bone. The differential expression of PXR and its target genes in cancer tissues has been suggested to determine the prognosis of chemotherapeutic outcome. In addition, the emerging evidence points to the implications of PXR in regulating apoptotic and antiapoptotic as well as growth factor signaling that promote tumor proliferation and metastasis. In this review, we highlight the recent progress made in understanding the role of PXR in cancer, discuss the future directions to further understand the mechanistic role of PXR in cancer, and conclude with the need to identify novel selective PXR modulators.

Keywords

PXR; Cancer; Drug resistance; Endocrine disruption; Dog

1. Introduction

PXR is a member of the nuclear receptor superfamily of ligand-activated transcription factors that regulate the expression of their target genes by binding to the gene's promoter (Fig. 1B). PXR is an orphan nuclear receptor that is activated by binding to various chemically and structurally distinct endobiotics and xenobiotics [1,2], including clinically-used chemotherapeutic drugs (tamoxifen, doxorubicin, taxol, and vincristine) [3–5] and environmental chemicals (bisphenol A) [6,7]. Similar to steroid receptors, PXR protein contains a DNA-binding domain (DBD), a hinge region (H), a ligand-binding domain (LBD), a ligand-dependent transactivation function 2 (AF-2) (Fig. 1A). In contrast to most

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nuclear receptors, PXR does not have a ligand-independent activation function 1 domain (AF-1) (Fig. 1A).

In the absence of an agonist, PXR is associated with transcriptional corepressors such as nuclear receptor corepressor 1 (NCoR1) and NCoR2 [1,8–10], which mediate repression of PXR basal transcription activity through the recruitment of histone deacetylases [10] (Fig. 1B). Agonists such as rifampicin, SR12813, pregnenolone 16α carbonitrile (PCN), anticancer drugs, and environmental chemicals [1–7] bind to PXR and induce conformational changes that lead to dissociation of corepressors and recruitment of coactivators such as steroid receptor coactivator 1 (SRC-1) and SRC-3 which have intrinsic histone acetyltransferase activity, (Fig. 1B) [1,8–10], resulting in chromatin remodeling and subsequent transcriptional activation [1]. Ligand-bound PXR binds to the promoter of its target gene as a heterodimer with retinoid X receptor α (RXRα), and the heterodimer can form in the absence of the promoter [11].

PXR regulates proliferation of both cancer and non-cancer cells. PXR is essential for normal progression of liver regeneration [12] and activation of PXR induces hepatic proliferation or inhibits apoptosis through multiple mechanisms [13–16]. On the other hand, PXR induces osteoclast apoptosis [17–19], suggesting that the mechanisms for regulation of cell proliferation by PXR are tissue and cell-specific. Similarly, in cancer cells, PXR regulates cell growth in a variety of cancer tissues (e.g., colon, ovarian, prostate, endometrial, osteosarcoma) [20–38] through multiple mechanisms. Additionally, PXR is involved in regulating metastasis of cancer cells [26,32,35].

PXR also alters therapeutic response of cancer cells to anticancer drugs by regulating the expression of drug metabolizing enzymes and drug transporters. This is evident in a variety of cancers, including breast, prostate, ovarian, colon and endometrial cancer [20–42]. Furthermore, PXR regulates the expression of the proteins involved in apoptosis and antiapoptosis in these cancers,which further contributes to altered tumor growth and drug sensitivity [24,30–32,43]. In this review, we summarize the recent progress made to comprehend the role of PXR in tumor development and progression, as well as in anticancer drug resistance, of both reproductive and non-reproductive tissue cancers.

2. Role of PXR in cancer

2.1. Breast cancer

The expression of PXR in human breast tissue appears to be driven by the cellular context. This is evident by differential expression of PXR in normal or cancerous tissue [20–24,39]. For instance, while some studies reported PXR expression exclusively in cancerous tissues [21,22], another study [20] reported PXR expression in both cancerous and adjacent normal tissues. On the other hand, the other report provided evidence for higher PXR expression in cancerous tissue than in adjacent normal tissue [23]. Notably, PXR expression was found to be higher in invasive stage than in early phase of breast cancer patients [21]. Likewise, higher PXR expression was found to be related to breast cancer progression [22]. These observations indicate that PXR expression may be context-specific and may play a role in development and progression of breast cancer.

Several reports show that PXR can induce cell proliferation in human breast cancer cells [20–23,39] through multiple cancer cell mediated mechanisms. While organic anion-transporting polypeptide-A (OATP-A) was found to be expressed exclusively in breast carcinoma cells [21], higher expression of organic anion-transporting polypeptide 1A2 (OATP1A2) was observed in the cancerous tissue than in adjacent normal tissue [23]. In the latter study, activation of PXR in T47-D breast cancer cells with rifampicin upregulated the

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expression of OATP1A2 and OATP1A2-mediated estrogen uptake as well as enhanced estrogen-dependent cell proliferation. Conversely, inhibition of PXR with A-792611 or knockdown of PXR with siRNA, resulted in downregulation of OATP1A2 expression as well as OATP1A2-mediated estrogen uptake. These observations support a possible role for PXR in breast tumor growth by enhancing the uptake of estrogens via OATP, thereby increasing intracellular levels of estrogens that activate estrogen receptor (ER).

In addition, it is interesting to note a significant correlation between PXR expression and ER status in breast cancer. Miki et al. [21] noticed a positive correlation, with higher PXR labeling index in ER-positive tumors. Additionally, higher PXR expression was found to be positively associated with lymph node status, histologic grade, Ki-67 proliferation marker, and p450 aromatase (estrogen synthase) expression in ER-positive cases [21]. In contrast, Dotzlaw et al. [20] and Conde et al. [22] found an inverse relationship between PXR expression and ER status, that is, the level of PXR expression was higher in ER-negative tumors. Even in the context of inverse relationship, PXR could contribute to growth in breast cancer cells because of the fact that estrogen binds and activates PXR, suggesting that estrogen may act through PXR in ER-negative tumors, thereby, inducing growth. Notably, in an MMTVneu mouse model of breast cancer, there is a marked increase in PXR-mediated estriol-induced mammary tumors [44]. These data support the role for PXR in inducing breast tumors through multiple mechanisms. The overall implications of these data show a significant trend supporting the anti-apoptotic role for PXR in breast cancer.

However, a study by Verma et al. [24] provided contrary evidence showing that PXR induces apoptosis in breast cancer cells. Activation of PXR with rifampicin, tamoxifen, anandamide, clotrimazole and nifedipine inhibited the proliferation of MCF-7 and ZR-75-I human breast cancer cells by inducing cell cycle arrest at the G1/S phase followed by apoptosis [24]. Likewise, overexpression of constitutively active PXR decreased the growth of MCF-7 cells [24]. Conversely, PXR knockdown using the targeted siRNA blocked PXR activation-induced apoptosis of MCF-7 cells, suggesting that PXR activation can control the growth of and induce apoptosis in breast cancer cells [24]. This study further demonstrated that PXR activation resulted in the up-regulation of inducible nitric oxide synthase (iNOS) and NO-dependent up-regulation of p53 and p53 target genes; P21, BAX and PUMA, with eventual cell arrest and apoptosis of breast carcinoma cells.

In addition to its role in tumor growth and progression, PXR has implications in breast cancer drug resistance via induction of drug metabolizing enzymes/drug transporters [20–23,39]. For instance, in MDA-MB-231 and MCF-7 human breast cancer cells, preactivation of PXR by SR12813, led to an increased resistance to Taxol as well as an increased expression of CYP3A4 and MDR1 [39]. Conversely, knockdown of PXR using small hairpin RNA (shRNA) sensitized MDA-MB-231 and MCF-7 cells to the treatment of Taxol, vinblastine or tamoxifen [39]. In another study [21], MDR1 was found to be expressed only in human breast carcinoma cells but not in non-neoplastic cells. 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 [22]. The overall implications of these data support that PXR confers resistance toward chemotherapy in breast cancer.

2.2. Endometrial cancer

PXR has implications in endometrial cancer growth and drug response. Variable levels of PXR expression has been noticed exclusively in human endometrial cancer tissues but not in normal tissues [34]. Additionally, the cancer tissues with higher PXR expression showed higher expression of CYP3A4 [34], suggesting that PXR may play a role in both tumor

growth and anticancer drug resistance. Indeed, Masuyama et al. [35] showed that downregulation of PXR by small interfering RNA (siRNA) in HEC-1 human endometrial cancer cells decreased the expression of both CYP3A4 and MDR1 and enhanced growth inhibition and apoptosis in the presence of paclitaxel and cisplatin, indicating that downregulation of PXR sensitizes endometrial cancer cells to chemotherapeutics. Conversely, overexpression of PXR led to significant decrease in cell growth inhibition and apoptosis in the presence of paclitaxel and cisplatin, suggesting that overexpression of PXR promotes tumor growth as well as increases resistance of endometrial cancer cells to chemotherapeutics.

2.3. Prostate cancer

Differential expression of PXR was observed in human prostate tissues, with higher PXR expression in cancerous tissues when compared with normal tissues [25,40]. PXR expression was also detected in PC-3, LNCaP and DU145 human prostate cancer cell lines [25]. In PC3 cells, activation of PXR with SR12813 enhanced the expression of both CYP3A4 and MDR1 and increased the resistance of PC-3 cells to anticancer drugs, paclitaxel and vinblastine, suggesting that PXR activation confers prostate cancer cells with increased resistance toward chemotherapy. On the other hand, the targeted knockdown of PXR using shRNA increased the sensitivity of PC3 cells to paclitaxel and vinblastine, suggesting that downregulation of PXR sensitizes prostate cancer cells toward chemotherapy. Conversely, another study [40] reported that higher PXR expression was correlated with increased survival rate of prostate cancer patients, suggesting that PXR may be a strong prognostic indicator of favorable outcomes and a therapeutic target in prostate cancer.

2.4. Ovarian cancer

There is clinical evidence to support the role of PXR in ovarian tumor aggressiveness and drug resistance. Gupta et al. [26] showed that PXR was expressed in human ovarian cancer tissues and was overexpressed in SKOV-3 and OVCAR-8 human ovarian cancer cell lines. In SKOV-3 cells, activation of PXR with rifampicin induced the expression of CYP3A4 and UGT1A1. In addition, PXR activation induced the proliferation of SKOV-3 cells *in vitro* and SKOV-3 mouse xenografts *in vivo*. Furthermore, PXR activation in SKOV-3 cells conferred resistance to anticancer drugs paclitaxel, ixabepilone and SN-38, indicating that activation of PXR induces both tumor growth and chemoresistance in ovarian cancer cells. Yue et al. [27] observed a significant negative relationship between PXR protein status and clinical outcome in patients with ovarian cancer, that is, PXR-positive status is negatively correlated with disease free survival as well as overall survival. Furthermore, PXR was found to be a significant risk factor for both disease-free survival and overall survival, suggesting that PXR may be a useful marker to identify ovarian cancer patients at risk of tumor recurrence or death.

2.5. Colon or colorectal cancer

Several studies have demonstrated that PXR promotes growth and metastasis as well as drug resistance in colon/colorectal cancer. Wang et al. [32] showed that PXR activation induced proliferation, invasion, and migration of LS174T human colon cancer cells *in vitro* and mouse xenografts of LS174T cells. In contrast, PXR knockdown inhibited proliferation and metastasis to liver from spleen, suggesting that PXR activation can enhance tumor growth and metastasis. Notably, the same group also demonstrated that PXR induced growth factor FGF19 [45] signaling to promote growth and metastasis of LS174 cells. Another study [30] showed that PXR activation inhibited deoxycholic acid (DCA)-induced apoptosis in HCT116 human colorectal cancer cells as well as staurosporine-induced apoptosis in LS180 human colon adenocarcinoma cells. The antiapoptotic effect of PXR was found to be

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associated with upregulation of multiple antiapoptotic genes including BAG3, BIRC2, and MCL-1. On the other hand, the expression of proapoptotic genes including BAK1 and P53 was downregulated, suggesting that PXR activation prevents induction of apoptosis in the colon cancer cells similar to the findings observed in hepatocytes [43]. It was also shown that PXR activation sensitizes human colon cancer cells to oxidative stress [31], which may have implications in the growth and promotion of colon cancer cells.

The other study [33], however, reported that the expression of PXR was lost or greatly diminished in many colon tumors, and that overexpression of PXR significantly inhibited the proliferation of HT29 human colon cancer cells. In addition, PXR significantly suppressed HT29 xenograft tumor growth in mice as a consequence of inhibited cancer cell proliferation, resulting from cell cycle arrest at G0/G1 phase accompanied by elevated p21 expression and inhibited E2F1 expression. Although this report supports anti-proliferative role for PXR, the overall trend supports proliferative, metastatic and antiapoptotic role for PXR in sporadic colon cancer. More recent literature is supportive of these findings as human PXR agonists increase metabolic clearance of 1a, 25-OH Vitamin D3 thereby attenuating any protective effects of this hormone in LS180 cells [46]. Similarly, the PXR promoter is significantly silenced by methylation in normal colon cells as opposed to tumor cells [47].

Anti-cancer drugs, including PXR activator doxorubicin, induced MDR1 expression in LS180 cells [28]. 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 anticancer drugs induce chemoresistance by activation of PXR [28]. Similarly, activation of overexpressed PXR in LS174T cells induced CYP3A4 expression and increased chemoresistance to irinotecan (CPT-11) and SN38 [29]. Conversely, knockdown of overexpressed PXR with shRNA reduced CYP3A4 induction and reversed chemoresistance to SN38, suggesting that PXR expression in colorectal cancer cells could interfere with the sensitivity and metabolism of drugs used in the treatment of colorectal cancer.

2.6. Other cancers

PXR also has implications in the growth/chemoresistance of other cancers [48–50]. For example, in osteosarcoma, PXR activation reduced the therapeutic effectiveness of etoposide, suggesting that PXR activation confers chemoresistance in osteosarcoma [38]. In Barrett's esophagus patients, higher nuclear PXR expression was detected in high-grade dysplasia than in low-grade dysplasia, suggesting that PXR may have a role in neoplastic progression in Barrett's esophagus [51]. Similarly, PXR expression was markedly higher in esophageal squamous carcinoma tissue compared with non-neoplastic esophagus [52]. However, higher nuclear PXR expression was also correlated with favorable clinical outcome of the patients with esophageal squamous carcinoma, suggesting that PXR might serve as a prognostic indicator in human esophageal squamous cell carcinoma [52]. These observations support a context-specific role for PXR in esophageal cancer.

3. Future directions

Consistent with the role of PXR in cancer, numerous mechanisms may be involved in PXR-mediated tumor growth or drug response. Identifying all the mechanisms will be critical to systematically dissect the role of PXR in tumor progression or suppression as well as chemoresistance or chemosensitivity. For example, PXR activation induces steatosis and many induced lipogenic pathway targets like fatty acid transporter CD36 are indeed implicated in malignancy [53–55]. Future studies need to be focused on comprehensively identifying the PXR target genes with oncogenic or tumor suppressor nature in a cell/

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context-specific manner [56]. It is equally important to investigate how PXR is regulated in a cell or context-specific manner in cancer. It is important to note that PXR has been shown to be regulated by epigenetic mechanisms including noncoding RNAs [57], promoter methylation [47,58], and protein arginine methyl transferase 1 [59]. However, it is unknown whether PXR regulates epigenetic mechanisms and investigation of such mechanisms will be useful to therapeutically target PXR in PXR expressing cancers.

PXR activation has been shown to disrupt endocrine homeostasis [60,61]. More importantly, several environmental endocrine disrupting chemicals activate PXR at clinically relevant concentrations [6,7,62–80]. Additionally, recent studies indicate a growing correlation between high exposure to endocrine disruptors (e.g., bisphenol A, xenoestrogens, polycyclic aromatic hydrocarbons) and cancer risk or drug response [75,81–87]. Although, the molecular pathways governing the tissue-specific phenotypes mediated by chronic exposure to endocrine disruptors are varied, it is clear that some important effects are mediated via PXR. Therefore, it is vital to understand the role of PXR in linking environmental chemicals to cancer. We expect to see rigorous scientific investigations focused on establishing a relationship between environmental chemicals that activate PXR (i.e., endocrine disruptors) and cancer [88].

PXR exhibits species specificity at both the ligand-binding and signaling-cascade levels [89,90]. PXR humanized mouse is a very useful animal model to address species specificity at the ligand-binding level [13,91]. However, no animal model is available to address species specificity at the signaling-pathway level. An immunodeficient mouse with induced-cancer is also a very useful model to study the role of PXR in cancer. However, it is possible that the signaling pathways in induced-cancer mice models could be considerably different from spontaneously developed natural-cancers in humans. Dog PXR has been shown to be similar to human PXR in terms of ligand-binding, that is, dog PXR is activated by both rifampicin and SR 12813 but not PCN [92]. Moreover, dogs live in the same environment as humans and harbor naturally-occurring cancers in many ways identical or similar to naturally-occurring human cancers. Therefore, dog may be included as an intermediate model to study the role of PXR in cancer. Dog cancer models may prove particularly valuable to study the carcinogenic effects of environmental chemicals that activate PXR to induce cancer growth and chemoresistance in humans [75,81–87]. Recently, there is an increasing awareness in the scientific community about the significance of dog cancer models as a powerful tool for advancing comparatively oncology studies [93,94]. It is now practically feasible to incorporate dog models for comparative oncology studies and is largely because of the availability of canine genome sequence and comparative oncology consortium tissue bank [93,94].

It has been shown for several nuclear receptors that they induce a phenotype that is tissue and context (isoform) specific. For example, ERRα [95,96], LXR [97], DAX-1 [98], NOR-1 [99] and CAR [100–103], induce cell proliferation and inhibit apoptosis in a variety of tissue systems. However, other receptors like Nurr77 [104,105], LRH-1 [106], SHP [107], PPARγ [108–111] and FXR [112] induce cell cycle arrest and apoptosis. Isoform specific effects are distinct, in that, ERRβ [113] and ERRγ [114] unlike ERRα, induce growth arrest in prostate cancer cells. Tissue specific effects of the same receptor, for example, LXR [97], is observed in smooth muscle cells versus breast cancer. In the latter tissue, LXR induces apoptosis as a consequence of estrogen deprivation [115]. Similarly, another receptor, TR-3 induces cell growth in lung cancer cells through MEKK activation [116] but induces apoptosis in prostate cancer cells through up-regulation of E2F1 [117]. PPARγ [108–111] induces apoptosis in a variety of cancer cell lines but PPARδ [118] induces cell proliferation through cyclin E1-dependent mechanisms. This effect of PPARδ [119] is controversial as other reports suggest that the receptor inhibits cell proliferation in other cell lines (e.g.,

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keratinocytes). The differential effects of PXR observed in different cancer tissues might be contributed by different isoforms/alternative splice variants of PXR [20,22,120].

There are at least three PXR isoforms (i.e. PXR.1, PXR.2 and PXR.3) defining PXR transcripts in mammalian cells [120–123]. These isoforms exhibit differential expression, ligand binding affinity and transcriptional activity. For example, the mouse PXR variant orthologous to human PXR.3 was less well activated than mouse PXR.1 by dexamethasone [1]. Likewise, human PXR.2, exhibits significantly diminished ligand-activated transcriptional activity because ligands do not bind the LBD of PXR.2 effectively [123]. Two studies provided the evidence for differential expression of PXR.1 and PXR.2 in human breast cancer [20,22]. Notably, Dotzlaw et al. [20] reported that MCF cells, with a low metastatic potential, expressed PXR.1 but not PXR.2 mRNA. However, MDAMB-231 cells, with a high metastatic potential, showed highest levels of both PXR.1 and PXR.2 mRNA [20]. These observations are tempting to speculate that differential expression of PXR isoforms might influence breast cancer progression. Tumor-specific regulation of isoforms or splice variants of some proteins has been reported to have very significant functional consequences [124]. Indeed, the spliced murine PXR, $mPXR_{\Delta 171–211}$, exhibits repressive action rather than activation [125]. Identifying isoforms and spliced variants in human tumors and non-tumor tissues would be a critical first step towards defining the importance of the isoforms and variants of PXR in human cancer.

In keeping with this theme, spliced variants of PXR might favor selective binding to coregulators in these tissues. Thus a complete definition of coregulator expression and binding to PXR in specific tissues (e.g., tumors) would also be needed to comprehensively understand the effects of PXR activation. For example, in breast cancer, while it has been noted that PXR expression portends a favorable prognosis [24], another report suggests that nuclear localization of both PXR and RXR-alpha portends a poor prognosis [22].

Furthermore, it is now well known that PXR undergoes posttranslational modifications that affect its activity [90,126–128], and that it is possible that even though PXR is expressed in some tumors, it may not be active and be activated by ligands (the converse could also be true). Receptor cross-talk (e.g., PXR and AhR or LXR/FXR or CAR) should also be given consideration, especially for those receptors that share common ligands (e.g., T1317 activates both PXR and LXR). Indeed, some receptors like AhR have been shown to phenocopy the effect of PXR in tumors [129,130]. In this regard, the study of PXR in tumor immunology might also be of interest, given that endogenous AhR activation by constitutive tryptophan catabolism suggests that there could be potential endobiotics that might trigger PXR activation or repression *in vivo*.

The other important aspect for the study of these receptors in cancers is tissue-context. For example, defining the role of PXR in sporadic tumors might not necessarily signify a unifying role of this receptor in cancer. For example, there are many subsets of tumors where receptors function in an opposing manner – in inflammatory bowel induced colon cancer, loss of adenomatous polyposis coli is a late event, while p53 mutations occur early in its pathogenesis [131,132]. The opposite is true for sporadic colon tumors. Indeed, many transcription factors have dual roles that are context dependent (e.g., GADD45beta, c-Myc) [133–135]. The same receptor may function in opposing manner in different tissues (e.g., androgen receptor in breast and prostate cancer as well as within subtypes of prostate cancer) [136]. Similarly, *in vitro* studies for apoptosis, senescence, autophagy or other forms of cell death like necroptosis, might also not replicate *in vivo* effects [137–139]. Thus a complete examination of both *in vitro* and *in vivo* effects is warranted in a tissue and context specific manner.

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Finally, the tissue specific phenotypes of PXR may vary considerably. For example, it remains unclear to what extent PXR induces metabolic phenotypes (e.g., lipogenesis, gluconeogenesis) in tissues other than liver [140]. Indeed, PXR's effect on cancer specific metabolism is unknown. Lipogenesis has been associated with cancer development [141] and drug resistance [142,143]. Species specificity of phenotypes must also be clarified (e.g., hepatic hypertrophy versus hyperplasia) [14] to determine whether humans are indeed subject to similar phenotypes [144].

In order to achieve these goals, significantly better reagents are needed for the study of PXR protein and protein modifications. The commercially available antibodies require significant optimization and quality control. Better antibodies for immunoprecipitation and immunoblots are required. Furthermore, somatic (genetic) deletion models for PXR and other receptors would also be welcome additions towards controls. Thus significant more work is needed to fully define all aspects of PXR function in tumors; however, the pace of research is progressing and as better reagents are available, we should be able to define its role.

4. Conclusion

The role of PXR in malignancy and chemoresistance may be tissue/context specific. For example, while PXR induces prostate cancer drug resistance, it has also been shown to be a favorable prognostic marker [36,40]. Likewise, in breast cancer cells, while PXR induces apoptosis, [24], it has also been shown to induce proliferation [21–23]. Similarly, in Barrett's esophagus and esophageal cancer, it remains controversial as to whether PXR predicts for poor or good prognosis [51,52,145]. Similarly, in colon cancer, depending on the cell type, PXR activation may induce cell cycle arrest [33,146]. Several mechanisms have been proposed for PXR-mediated effects in cancer and include regulation of the genes involved in cell proliferation, metastasis, proapoptosis, apoptosis, antiapoptosis, drug metabolism, drug transport, and endocrine homeostasis as well as regulation of reactive oxygen species system (Fig. 2) [20–43].

PXR has been proposed as a therapeutic target in treating several human diseases including cancer. Depending on the cancer tissue or cellular context, PXR activation or inhibition has been shown to exert anticancer phenotypes (i.e. sensitize the cancer cells to anticancer drugs, prevent induction of drug resistance, induce apoptosis or reduce proliferation, invasion and migration of the cancer cells). Currently, there are several small molecules [1–5,29,41,147–154] available to either activate or inhibit PXR function in cancer cells. However, there are no selective PXR modulators, which are expected to display differential activities compared to the natural ligands and retain tissue-selective agonist or antagonist activity. Therefore, identification of selective novel small molecule modulators of PXR will be tremendously beneficial to improve the therapeutic outcomes of PXR expressing cancers. Synthetic ligands for PXR can be identified through high throughput screening approaches. The lead structures can be optimized further to adjust the properties of the compounds to appropriately modulate the activities of PXR. Identification of such novel, tissue-selective synthetic modulators, with minimal or no unwanted side activities, would prove extremely valuable to treat PXR expressing cancers.

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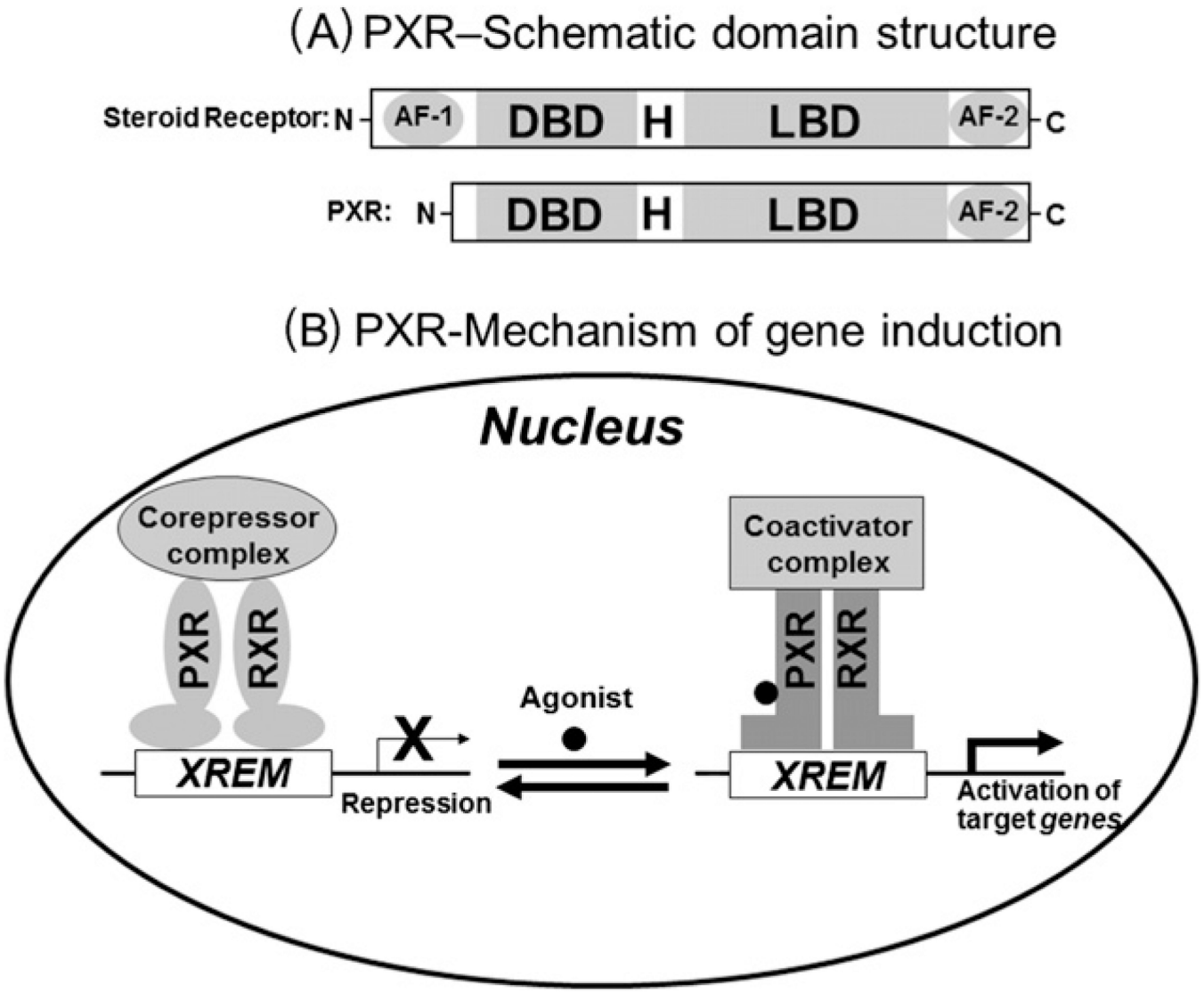

Fig. 1.

PXR structure and mechanism of target gene induction. (A) A schematic comparison of the domain structures of a steroid receptor and PXR. AF-1, activation function 1; DBD, DNA binding domain; H, hinge region; LBD, ligand binding domain; AF-2, transactivation function 2. (B) A current model of PXR-mediated gene regulation. PXR functions as heterodimer with retinoid X receptor (RXR). Agonist binding induces a dissociation of co-repressors, recruitment of co-activators and contributes to chromatin remodeling and transcriptional activation. XREM, xenobiotic responsive enhancer module.

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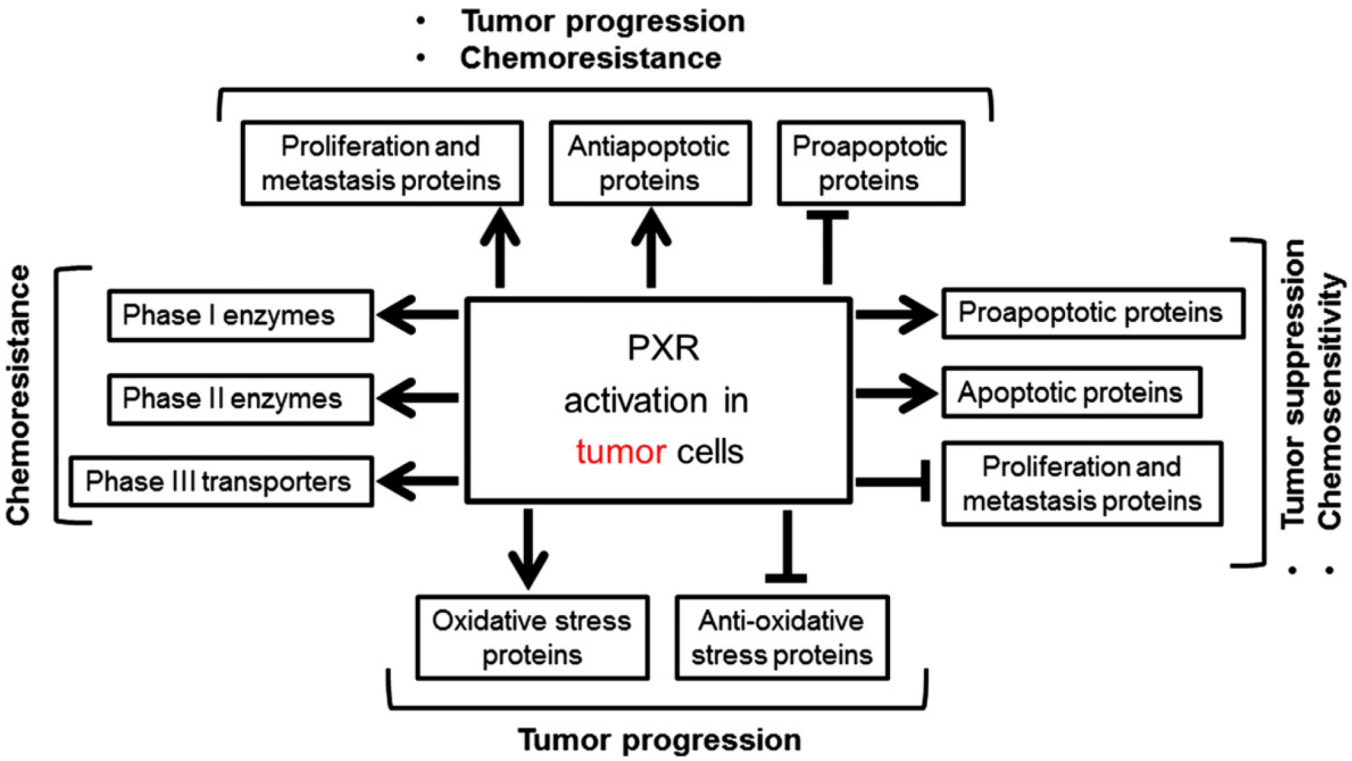

Fig. 2.

Consequences of PXR activation in tumor cells. Note that these PXR-mediated events are context and cell-specific depending on the cancer tissue. Arrows represent induction or activation; blunt arrows represent inhibition or repression.

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