J Endocrinol Reprod 14 (2010) 1 : 1-8 *Review Article*

Networking strategies and emerging roles of Pregnane & Xenobiotic Receptor (PXR) in normal and pathological states

Subodh Kumar and Rakesh K. Tyagi
Special Centre for Molecular Medicine, Jawaharlal Nehru University,
New Delhi – 110067, India.

Summary

The Pregnane & Xenobiotic Receptor (PXR), a member of the nuclear receptor family of ligand-activated transcription factors, is an integral component of the body's defense mechanism against toxic xenobiotics and endobiotic metabolites. Due to highly promiscuous nature and broad ligand specificity, this 'xenosensor' has emerged as a master-regulator of xenobiotic metabolism and regulator of all phases of drug metabolism and clearance. It has also been implicated to play an important role in induction of drug-drug interactions. During the past few years, research has unveiled some novel and mostly unanticipated roles for PXR in inflammation, lipid homeostasis, bone homeostasis, vitamin D metabolism, energy homeostasis, endocrine-related functions and cancer. Recent evidences have revealed existence of PXR cross-talk with several other cellular signaling pathways that profoundly expand the horizon of this promiscuous xenosensor. These cross-talks between PXR and other signaling pathways may elucidate molecular mechanisms to explain the involvement of PXR in several hitherto unanticipated physiological functions. The present article summarizes some of the important cross-talks of PXR with other nuclear receptors and different signaling pathways to describe how these cross-talks integrate into novel biological functions. It is anticipated that better understanding towards the mechanisms of PXR cross-talk might divulge novel therapeutic approaches to combat various diseases.

Key words : Cross-talk, drug metabolism, nuclear receptor, PXR, xenobiotics.

Introduction

The Pregnane & Xenobiotic Receptor (PXR; NR1I2, also known as SXR) is a member of the nuclear receptor superfamily of ligand-modulated transcription factors and a key regulator of genes involved in xenobiotic and endobiotic metabolism (Blumberg et al., 1998; Saradhi et al., 2006). Initially, PXR was reported to be expressed predominantly in the liver and intestine as a highly promiscuous receptor with broad ligand specificity (Blumberg et al., 1998). It is now reported to be activated by a variety of structurally-distinct ligands that are known to induce the expression of CYP450 genes central to drug metabolism. These compounds include phenobarbital, rifampicin, dexamethasone, nifedipine and several herbal drugs (Blumberg et al., 1998; Saradhi et al., 2006; Negi et al., 2008; Zhou et al., 2009). PXR is also known as the master-regulator of the genes involved in drug metabolism including CYP3A4 which in turn is involved in metabolism of more than 50% of clinical drugs (Saradhi et al., 2006; Zhou et al., 2009).

Substantial reports also suggest that the ligand specificity of PXR differs from species to species. For example, human and rabbit PXR could be activated by rifampicin unlike mice PXR. Additionally, PCN could efficiently activate mice PXR, but not the rabbit and human form (Xie and Evans 2001; Zhou et al., 2009). By acting as a ligand-activated transcription factor, PXR regulates all the critical steps of xenobiotic metabolism and transport and is also responsible for important inductive drug-drug interactions. The human and mouse PXR genes comprise 9 exons and encode proteins of 434 and 431 residues, respectively (Blumberg et al., 1998; Kliewer et al., 1998). In addition to the liver and intestine, expression of PXR is also reported in other tissues, including kidney, lung, testis, bone, breast tissue- normal and neoplastic- and peripheral blood mononuclear cells. Studies to determine the subcellular localization of PXR have provided conflicting results. Some reports suggest that human PXR in an exclusively nuclear protein irrespective of ligand binding (Koyano et al., 2004; Saradhi et al., 2005). However, there are some reports showing that in unliganded condition mice PXR remains in cytoplasm and upon activation by its agonist it translocates to nucleus (Squires et al., 2004). The discrepancies in these findings may be due to differences in the type of PXR employed (human *vs.* mouse) or *in vivo vs. in vitro* nature of the experiments. Recently, localization of PXR is also shown on to the mitotic chromatin which opens another area of research (Saradhi et al., 2005). These results indicate that subcellular

Correspondence to be addressed to: Dr. Rakesh K. Tyagi, Ph.D.; E.mail: rktyagi@yahoo.com, rkt2300@mail.jnu.ac.in

trafficking and mitotic chromatin docking may be an important regulatory process for the function of PXR.

The ligand-activated PXR forms a complex with its obligate heterodimeric partner Retinoid X Receptor α (RXR α; NR2B1), then binds response elements in the promoters and enhancers of target genes. These response elements usually take the form of direct (DR3, DR4) or averted (ER6) repeats of the consensus motif AG(G/T)TC(A/C). Activated PXR also induces the recruitment of coactivators such as SRC-1 and GRIP-1 and release of corepressor molecules like NCoR-1 and SMRT leading to the formation of active transcription complex and triggering the activation of PXR target genes. PXR is involved in all aspects of xenobiotic metabolism and disposition by regulating the transcription of many important drug metabolizing enzymes, including phase I oxidative enzymes such as CYP1A, CYP2B and CYP2C, CYP3A families; phase II conjugating enzymes such as carboxylesterases, alcohol dehydrogenase; glutathione-S-transferase, UDP-glucuronosyltransferase and sulfotransferase families; and phase III transporters such as p-glycoprotein (MDR1), several multi-drug resistance related proteins (MRPs), and organic anion transport protein 2 (OATP2) (Kliewer et al., 2002; Saradhi et al., 2006) (Fig. 1). Since, PXR plays pivotal role in all stages of xenobiotic metabolism and transport, and is responsible for induction of drug-drug interactions, this promiscuous chemical sensor is considered as the 'master-regulator' of xenobiotic metabolism and transport.

Multifaceted PXR: more than a xenosensor

Although the role of PXR is clearly established as a 'xenosensor' in regulation of drug metabolism-related genes, the subsequent functions in other tissues remain ambiguous. Consistent with its role in regulating enzymes and transporters involved in eliminating potentially harmful substances, PXR is primarily expressed in liver and intestine. However, recent observations suggest that PXR is also expressed at lower level in lung, stomach, prostate, uterus, ovary, placenta, breast, osteoclasts, heart, adrenal gland, bone marrow and specific regions of the brain, peripheral blood monocyte and the blood–brain barrier (Lamba et al., 2004; Bauer et al., 2004; Orans et al., 2005; Saradhi et al., 2006; Zhou et al., 2009). Expression in other tissues which are not primarily involved in drug metabolism indicates that PXR might be playing some distinct function in these tissues. Several emerging avenues of research have revealed novel and mostly unanticipated roles for PXR in inflammation, bone homeostasis, vitamin D metabolism, energy homeostasis, endocrine disruption, T lymphocyte function and cancer (Staudinger et al., 2001; Stedman et al., 2005; Tabb and Blumberg, 2006; Saradhi et al., 2006; Zhou et al, 2009; Dubrac et al., 2010) (Fig. 2). Some recent reports on PXR up-regulation in certain malignancies (colon, breast, prostate, endometrial, esophagus, ovarian cancer, etc.) suggest hitherto unexplained role of PXR in these cancerous conditions (Doltzlaw et al., 1999; Masuyama et al., 2003; Chen et al., 2007; Gupta et al., 2008; Verma et al., 2009; Takeyama et al., 2009). Studies aimed at determining the significance of PXR expression in these malignancies are not clear and have provided conflicting results. There are reports that indicate PXR to be an inducer of cancer proliferation or implicate it in imparting increased metabolism and reduced clinical efficacy of some anticancer drugs. Other reports also designate a protective role for PXR through suppression of cancer proliferation, especially in endocrine-related cancers (Dotzlaw et al., 1999; Masuyama et al., 2003; Chen et al., 2007; Gupta et al., 2008; Verma et al., 2009; Takeyama et al., 2009). These results suggest that PXR has some important functions in body that remain to be fully explored.

Transcriptional cross-talk : An alternative mode of PXR action

Although the overall scheme of PXR-mediated gene regulation appears to be relatively simple, a number of evidences now suggest that PXR signaling also modulates several other transcription factors including other member of nuclear receptors. Similarly, these signaling molecules also modulate PXR-mediated gene regulation. The phenomenon of this cross-regulation by which PXR transcriptional activity is modulated by other signaling molecules is commonly known as 'transcriptional cross-talk' (Gottlicher et al., 1998; Pascussi et al., 2004, 2008). In other words, transcriptional cross-talk refers to a close encounters between the two or more distinct pathways where one signal affects the transcriptional output of another. Depending upon specific function and status of differentiation, cross-talks can integrate into two types of responses, synergistic or inhibitory. There are mounting evidences suggesting that a multitude of functionally diverse signaling molecules cross-talk with PXR and regulate each other's transcriptional activity in a context-dependent manner (Table 1). Evidences suggest that these cross-talks can occur at various level of PXR signaling involving different mechanisms: First, at ligand-binding level where a ligand molecule may bind and activate two different nuclear receptors (i.e., PXR/CAR) (Xie et al., 2000). In addition, some ligands which are agonists for a given nuclear receptor may behave as antagonist for

another receptor PXR (i.e., PXR/AR) (Kumar, 2010). Second, at DNA binding level, where two different nuclear receptors may share the same response element (i.e., PXR/VDR) (Pascussi et al., 2005). Third, at receptor level, where PXR may interact with other transcription factors/signaling molecules in such a way that one of them behaves as a coactivator or a corepressor of the other (i.e., PXR/NFκB, PXR/FOXO1 and PXR/AR) (Zhou et al., 2006; Nakamura et al., 2007; Kumar, 2010). These evidences of PXR cross-talks with other signaling pathways suggest that the expression of a specific set of target genes expected to be regulated by PXR are in fact dependent on a complex network of regulatory pathways. Furthermore, PXR cross-talk with other signaling pathways also illustrates how this xenosensor may modulate diverse physiological functions in normal and pathological states.

Table 1- Cross-talk between PXR and other cellular signaling pathways

Transcription Factor	Mechanism/s involved	Physiological Effect(s)	References
CAR	**Shares ligands and activate common set of genes**	**Promotes xenobiotic metabolism**	**Xie et al., 2000**
FXR	**Shares ligands and activate overlapping set of genes**	**Promotes bile acid metabolism**	**Gnerre et al., 2004**
VDR	**PXR enhances expression of VDR target gene, CYP24**	**Enhances the metabolism of 1, 25(OH)2D3, leading to drug-induced osteomalacia**	**Pascussi et al., 2005**
TR	**Shares response elements**	**Enhances metabolism of thyroid hormone, decreased hormone level**	**Pascussi et al., 2008**
HNF4α	**PXR inhibits HNF4α transcriptional activity**	**Regulates gluconeogenesis and fatty acid homeostasis**	**Miao et al., 2006**
AR	**PXR represses AR transcriptional activity**	**Enhances repressive actions of antiandrogens**	**Kumar et al., unpublished observations**
SHP	**SHP inhibits PXR transcriptional activity**	**Controls bile acids homeostasis**	**Ourlin et al., 2003**
NFκB	**PXR represses NFκB activity**	**Controls inflammation**	**Zhou et al., 2006 Gu et al., 2006**
FOXO1	**FOXO1 induces PXR transcriptional activity**	**Controls gluconeogenesis**	**Kodama et al., 2004**
FOXA2	**PXR represses FOXA2 activity**	**Decreased fatty acid metabolism in fasting liver**	**Nakamura et al., 2007**

CAR- constitutive androstane receptor; **FXR**- fernesoid X receptor; **VDR**- vitamin D receptor; **TR**- thyroid receptor; **HNF4α**- hepatocyte nuclear factorα; **AR**- androgen receptor; **SHP**-small heterodimeric protein; **NFκB**- nuclear factor κB; **FOX**- forkhead box genes.

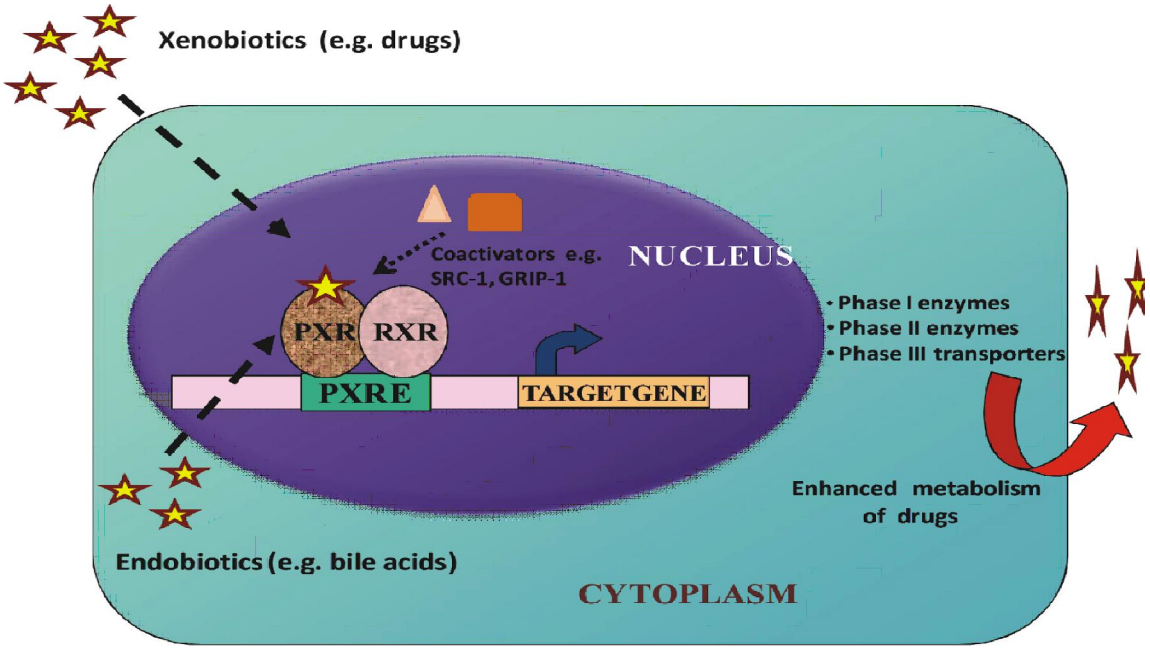

Fig. 1: Molecular mechanism of PXR action: PXR is activated upon binding to a large number of xenobiotics (e.g., clinical drugs) as well as many endobiotics (e.g., bile acids, steroids). Ligand-activated PXR binds to the regulatory region of its target genes as a heterodimer with RXR. Activated PXR also enhances co-activators recruitment (e.g. SRC-1, GRIP-1) and, finally, activates the transcription of target genes. The major target genes of PXR include enzymes involved in drug metabolism (i.e., Phase I enzymes, Phase II enzymes and Phase III transporters). These genes trigger not only the elimination of the given PXR activators (e.g., xenobitics and endobiotics) but may also induce drug-drug interactions.

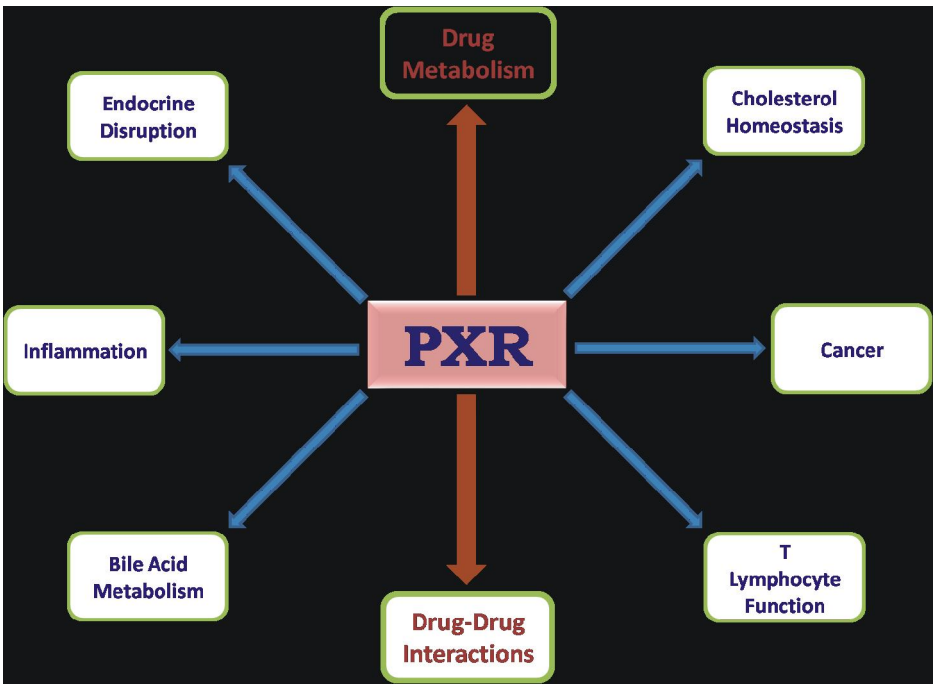

Fig. 2: Emerging roles of PXR: In addition to its established role in inducing xenobiotic metabolism and triggering drug-drug interaction, PXR has potential roles in various other biological functions including the regulation of lipid homeostasis, bone homeostasis, inflammation, endocrine disruption, T lymphocyte function and cancer.

PXR cross-talk with other nuclear receptors

Mounting evidences suggest that, in addition to directly regulating expression of its own target genes, PXR can cross-talk with other nuclear receptors to exert more complex effects on gene regulation. First example of such a cross-talk is with an important xenobiotic receptor, constitutive androstane receptor (CAR), a key regulator of many genes involved in drug metabolism including CYP2B2 and CYP2B10. Like PXR, it also plays a broad role in xenobiotic metabolism (Xie and Evans, 2001). Interestingly, PXR and CAR share a variety of ligands and activate an overlapping set of genes. For example, phenobarbital, a potent ligand of CAR, can also bind to and activate PXR. Furthermore, CAR can regulate CYP3A genes through PXR response elements, and PXR can regulate CYP2B genes by binding to phenobarbital response element, PBRE (Xie et al., 2000). Consequently, PXR/CAR cross-talk integrates into a complex regulation of xenobiotic detoxification pathways. Another important example of PXR cross-talk is with fernesoid X receptor (FXR), which is an important regulator of bile acid homeostasis (Forman et al., 1995; Wang et al., 1999). PXR and FXR not only share ligands (i.e., bile acids, GW4064) but they also regulate some common target genes. FXR has been shown to activate PXR target gene CYP3A, and similarly PXR also cross-activates some FXR target genes such as SULT2A1 and MRP2 (Gnerre et al., 2004). Furthermore, FXR ligand GW4064 also induces the mRNA level of PXR (Jung et al., 2006). The cross-talk between PXR and FXR provides a mechanism towards efficient protection of the liver against bile acid-induced toxicity. In addition, bile acid-activated FXR is also an important regulator of another orphan nuclear receptor, small heterodimeric partner (SHP). SHP has been shown to directly interact with PXR and repress PXR transcriptional activity (Ourlin et al., 2003). Furthermore, PXR also regulates the expression of SHP (Frank et al., 2005). Another level of regulation of bile acid homeostasis is documented by cross-talk between PXR and HNF4α. It has been demonstrated that activated PXR directly interacts with HNF4α that subsequently leads to inhibition of CYP7A1 gene transcription (Bhalla et al., 2004). Since HNF4α is involved in regulation of genes involved in gluconeogenesis and fatty acid homeostasis, PXR/HNF4α cross-talk may play a key role in the regulation of these biological phenomena. Collectively, these data suggest that PXR/FXR, PXR/SHP and PXR/HNF4α cross-talks play an important role in regulation of bile acid homeostasis.

Vitamin D receptor (VDR) mediates the effect of 1α, 25-dihydroxyvitamin D_3 which is responsible for a number of biological functions, most notably bone mineralization (Kato, 2000). Recently, one study revealed the cross-talk between PXR and VDR and demonstrated that VDR is able to bind and transactivate the PXR responsive elements of CYP3A4, and similarly PXR activates VDR target gene CYP24 (Pascussi et al., 2005). Up-regulation of CYP24 leads to increased metabolism vitamin D and impairs bioavailability of vitamin D and bone mineralization, leading to drug-induced osteomalacia and osteoporosis (Pascussi et al., 2005).

In an attempt to study the role of PXR in regulation of endocrine functions, we studied the effect of PXR on androgen receptor (AR)-mediated function. We have shown that antiandrogens exert inverse response to AR and PXR transcriptional activity (Kumar et al., unpublished observation). We have demonstrated that antiandrogens and endocrine disruptors, which are potent antagonists of AR transcriptional activity, also behave as agonists of PXR activity and *vice versa*. Furthermore, we have also shown that PXR directly interacts with AR and inhibit AR transcriptional activity and revealed that PXR is a key determinant in antiandrogen-mediated repression of AR activity. Since AR plays a key role in prostate cancer development, these observations of PXR/AR cross-talk suggest a novel role of PXR in this malignancy. PXR/AR cross-talk also revealed an unexplored functional relationship between xenobiotic regulation and endocrine-related functions (Kumar et al., unpublished observations).

Cross-talk between PXR and several other nuclear receptors, including liver X receptor (LXR), estrogen receptor α (ERα), thyroid receptor (TR), glucocorticoid receptor (GR) and PPARγ, has been described (Pacussi et al., 2004, 2008; Zhou et al., 2009). Collectively, it appears that cross-talks between PXR and other members of nuclear receptor family integrate into a complex regulation of PXR-mediated gene regulation and play a key role in various biological functions such as xenobiotic metabolism, lipid homeostasis and endocrine-related functions.

Networking of PXR with other signaling pathways

In addition to cross-talk with other nuclear receptor, PXR has been also reported to have interplay with several other signaling pathways and transcription factors such as NFκB, FoxO1 and FoxA2. Transcription factor NFκB is a key regulator of inflammation and oncogenesis (Karin and Greten, 2005). Several recent reports demonstrate an inhibitory cross-talk between PXR and NFκB (Zhou et al., 2006; Gu et al., 2006). PXR has been shown to be

negative regulator of NFκB-mediated signaling leading to the repression of inflammation-related genes. Similarly, NFκB also inhibits PXR target gene CYP3A4 (Zhou et al., 2006). Furthermore, physical interaction between PXR and NFκB has also been demonstrated (Gu et al., 2006). PXR/NFκB cross-talk also suggests the possible mechanism of immunosuppressive functions of many drugs (such as rifampicin), implying existence of a potential molecular mechanism that links xenobiotic metabolism and inflammation (Zhou et al., 2006).

FoxO1 and FoxA2 are members of the 'forkhead' family of transcription factors that play vital roles in lipid metabolism and gluconeogenesis in the liver. FoxO1 activates genes involved in gluconeogenesis that notably include phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P). Insulin negatively regulates FoxO1 and inhibits gluconeogenesis (Montminy and Koo, 2004). Recently, it has been reported that FoxO1 interacts with PXR and CAR and enhances their transcriptional activity. Interestingly, in the reciprocal cross-talk both PXR and CAR repress FoxO1 transcriptional activity by preventing its binding to its responsive element in its target gene such as PEPCK (Kodama et al., 2004). These results indicate that drug metabolism and gluconeogenesis are reciprocally regulated in response to insulin and/or xenobiotics. FoxA2 regulates the genes involved in ketogenesis and β-oxidation during fasting or after prolonged exercise (Wolfrum et al., 2004). Recently, it is reported that PXR can cross-talk with FoxA2 to mediate drug-induced repression of lipid metabolism in fasting mouse liver (Nakamura et al., 2007). These evidences of cross-talk between PXR and forkhead family of transcription factors reveal functional links between insulin and xenobiotic-mediated pathways with a key role in regulation of energy homeostasis.

In addition to above-mentioned cross-talks, PXR has been implicated in up-regulation of expression level of p53 and its target gene *via* iNOS pathway in breast cancer cells (Verma et al., 2009). Furthermore, cross-talk between some growth factor signaling pathways and PXR signaling has also been reported. For example, protein kinase C activators negatively regulate PXR transcriptional activation while protein kinase A activators induce PXR activity (Ding and Staudinger, 2004, 2005). In a similar study, IL-6 signaling is reported to negatively regulate PXR expression level (Pascussi et al., 2000). Taken together, these reports suggest a complex and precise regulation of PXR signaling *via* cross-talk with other signaling pathways. These cross-talks integrate into a complex regulation of many biological functions such as drug metabolism, lipid homeostasis, inflammation, energy homeostasis and cancer.

Concluding remarks

PXR plays a key role in regulating the metabolism and clearance of a large variety of endobiotic, dietary and xenobiotic chemicals. The expression of PXR in many other tissues, besides liver and intestine, suggests that it may have additional functions in the body which contribute to disease outcome in diverse clinical situations. Recent discoveries have unveiled some novel and mostly unanticipated roles of PXR in inflammation, lipid homeostasis, bone homeostasis, vitamin D metabolism, energy homeostasis, T lymphocyte functions, endocrine-related functions and cancer. Recent examples of transcriptional cross-talk of PXR with other signaling pathways have profoundly expanded the horizon of this promiscuous xenosensor. In view of the fact that multitude of biological partners functionally interact with PXR, xenobiotic signaling appears to be dependent on a very complex network of regulatory pathways. These molecular cross-talks may divulge multiple molecular mechanisms to explain involvement of PXR in many hitherto unknown physiological functions. Ultimately, an improved understanding of PXR cross-talks is expected to provide new avenues of pharmacological opportunities in many pathological conditions, most notably in areas of metabolic disorders and cancer.

Acknowledgments

We acknowledge the financial support from Department of Science and Technology (DST; SR/SO/bb-17/2006) and Council of Scientific and Industrial Research [CSIR; 37(1249)/06/EMR-II] for the projects related to the subject of this article. CSIR (NET) fellowship to Subodh Kumar is thankfully acknowledged.

References

Bauer B, Hartz, A , Fricker, G, et al. (2004). Pregnane X receptor upregulation of p-glycoprotein expression and transport function at the blood–brain barrier. *Mol Pharmacol*. **66:**413–419.

Bhalla S, Ozalp C, Fang S, Xiang L, Kemper JK (2004) Ligand-activated pregnane X receptor interferes with HNF-4 signaling by targeting a common coactivator PGC-1: Functional implications in hepatic cholesterol and glucose metabolism. *J Biol Chem*. **279:**45139-45147.

Blumberg B, Sabbagh W Jr, Jugulion H, Bolado J Jr , Van Meter CM , Ong ES, Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes. Dev*. **12:** 3195-3205.

Chen Y, Tang Y, Wang MT, Zeng S, Nie D (2007) Human pregnane X receptor and resistance to chemotherapy in prostate cancer. *Cancer Res*. **67:**10361-10367.

Ding X, Staudinger JL (2004) Repression of PXR-mediated induction of hepatic CYP3A gene expression by protein kinase C. *Biochem Pharmacol*. **69:**867–873.

Ding X, Staudinger JL (2005) Induction of drug metabolism by forskolin: the role of the pregnane X receptor and the protein kinase A signal transduction pathway. *J Pharmacol Exp Ther*. **312:**849–856.

Dotzlaw H, Leygue E, Watson P, Murphy LC (1999) The human orphan receptor PXR messenger RNA is expressed in both normal and neoplastic breast tissue. *Clin Cancer Res*. **5:**2103-2107.

Dubrac S, Elentner A, Ebner S, Horejs-Hoeck J, Schmuth M (2010) modulation of T lymphocyte function by the pregnane x receptor. *J Immunol*. **184**:2949-2957.

Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM, Weinberger C (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell* **81:**687-693.

Frank C, Makkonen H, Dunlop TW, Matilainen M, Vaisanen S, Carlberg C (2005) Identification of pregnane X receptor binding sites in the regulatory regions of genes involved in bile acid homeostasis. *J Mol Biol*. **346:** 505-519.

Gnerre C, Blattler S, Kaufmann MR, Looser R, Meyer UA (2004) Regulation of CYP3A4 by the bile acid receptor FXR: evidence for functional binding sites in the CYP3A4 gene. *Pharmacogenetics* **14:**635–645.

Gottlicher M, Heck S, Herrlich P (1998) Transcriptional cross-talk, the second mode of steroid hormone receptor action. *J Mol Med*. **76:**459-460.

Gupta D, Venkatesh M, Wang H, Kim S, Sinz M, Goldberg GL, Whitney K, Longley C, Mani S. (2008) Expanding the roles for pregnane X receptor in cancer: proliferation and drug resistance in ovarian cancer. *Clin Cancer Res*. **14:**5332-5340.

Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, Gallo MA, Xie W, Tian Y (2006) Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J Biol Chem*. **281:**17882-17889.

Jung D, Mangelsdorf DJ, Meyer UA (2006) PXR is a target of FXR. *J Biol Chem* **281:** 19081–19091

Karin M, Greten FR (2005) NF-kappaB: linking inflammation and immunity to cancer development and progression *Nat Rev Immunol*. **5:**749-759.

Kato S (2000) The function of vitamin D receptor in vitamin D action. *J Biochem. (Tokyo)* **127:**717–22.

Kliewer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterström RH, Perlmann T, Lehmann JM (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92:**73-82.

Kliewer SA, Goodwin B, Willson TM. (2002) The nuclear pregnane X receptor: a key regulator of xenobiotic metabolism. *Endocr Rev*. **23:**687-702.

Kodama S, Koike C, Negishi M, Yamamoto Y (2004) Nuclear receptors CAR and PXR cross talk with FOXO1 to regulate genes that encode drug-metabolizing and gluconeogenic enzymes. *Mol Cell Biol*. **24:**7931-7940.

Koyano S, Kurose K, Saito Y, Ozawa S, Hasegawa R, Komamura K, Ueno K, Kamakura S, Kitakaze M, Nakajima T, Matsumoto K, Akasawa A, Saito H, Sawada J. (2004) Functional characterization of four naturally occurring variants of human pregnane X receptor (PXR): one variant causes dramatic loss of both DNA binding activity and the transactivation of the CYP3A4 promoter/enhancer region. *Drug Metab Dispos*. **32:**149-154.

Kumar S (2010) *Regulation of androgen receptor: Transcriptional cross-talk and its implications in prostate cancer*. Ph.D., thesis, submitted to Jawaharlal Nehru University, New Delhi, India.

Lamba V, Yasuda K, Lamba JK, et al. (2004) PXR (NR1I2): Splice variants in human tissues, including brain, and identification of neurosteroids and nicotine as PXR activators. *Toxicol Appl Pharmacol*. **199:**251–265.

Masuyama H, Hiramatsu Y, Kodama J, Kudo T (2003) Expression and potential roles of pregnane X receptor in endometrial cancer. *J Clin Endocrinol Metab*. **88:**4446-4454.

Montminy M, Koo SH (2004) Diabetes: outfoxing insulin resistance? *Nature* **432:**958-959.

Nakamura K, Moore R, Negishi M, Sueyoshi T (2007) Nuclear pregnane X receptor cross-talk with FoxA2 to mediate drug-induced regulation of lipid metabolism in fasting mouse liver. *J Biol Chem.* **282:**9768–9776.

Negi S, Akbasha MA, Tyagi RK (2008) Clinical correlates in drug-herbal interactions mediated *via* nuclear receptor PXR activation and cytochrome P450 induction *J Endocrinol Reprod*. **12**:1-12.

Orans J, Teotico DG, Redinbo MR (2005) The nuclear xenobiotic receptor pregnane X receptor: Recent insights and new challenges. *Mol Endocrinol*. **19:**2891-2900.

Ourlin JC, Lasserre F, Pineau T, et al. (2003) The small heterodimer partner interacts with the pregnane Xr and represses its transcriptional activity. *Mol Endocrinol.* **17:**1693-16703.

Pascussi JM, Gerbal-Chaloin S, Drocourt L, et al. (2004) Cross-talk between xenobiotic detoxication and other signaling pathways: clinical and toxicological consequences. *Xenobiotica* **34:**633-664.

Pascussi JM, Gerbal-Chaloin S, Pichard-Garcia L, Daujat M, Fabre JM, Maurel P, Vilarem MJ (2000) Interleukin-6 negatively regulates the expression of pregnane X receptor and constitutively activated receptor in primary human hepatocytes. *Biochem Biophys Res Commun.* **274:**707-713.

Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, Pineau T, Saric J, Navarro F, Maurel P, Vilarem, MJ (2005) Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. *J Clin Invest.* **115:**77-186.

Pascussi JM, Gerbal-Chaloin S, Duret C, Daujat-Chavanieu M, Vilarem M, Maurel P (2008) The Tangle of nuclear receptors that controls xenobiotic metabolism and transport: Crosstalk and consequences. *Ann Rev Pharmacol Toxicol*. **48:**1-32.

Saradhi M, Sengupta A, Mukhopadhyay G, Tyagi RK (2005) Pregnane and Xenobiotic Receptor (PXR/SXR) resides predominantly in the nuclear compartment of the interphase cell and associates with the condensed chromosomes during mitosis. *Biochim Biophys Acta*. **1746:** 85-94.

Saradhi M, Kumar N, Reddy RC, Tyagi RK (2006) Pregnane and xenobiotic receptor (PXR): a promiscuous xensosensor with a role in human health and disease. *J Endocrinol Reprod.*. **10:** 1-12.

Squires EJ, Sueyoshi T, Negishi M (2004) Cytoplasmic localization of pregnane X receptor and ligand-dependent nuclear translocation in mouse liver. *J Biol Chem.* **279:**49307-49314.

Staudinger J, Liu Y, Madan A, Habeebu S, Klaassen CD (2001) Coordinate regulation of xenobiotic and bile acid homeostasis by pregnane X receptor. *Drug Metab Dispos.* **29:**1467-1472.

Stedman CA, Liddle C, Coulter SA, et al. (2005) Nuclear receptors ,constitutive androstane receptor and pregnane X receptor ameliorate cholestatic liver injury. *Proc Natl Acad Sci USA.* **102:**2063-2068.

Tabb MM, Blumberg B (2006) New modes of action for endocrine-disrupting chemicals. *Mol Endocrinol.* **20:**475-482

Takeyama D, Miki Y, Fujishima F, Suzuki T, Akahira JI, Hata S, Miyata G, Satomi S, Sasano H (2010) Steroid and xenobiotic receptor in human esophageal squamous cell carcinoma: A potent prognostic factor. *Cancer Sci.* **101:**545-549.

Verma S, Tabb MM, Blumberg B (2009). Activation of the steroid and xenobiotic receptor, SXR, induces apoptosis in breast cancer cells. *BMC Cancer* **9:**3

Wang H, Chen J, Hollister K, Sowers LC, Forman BM (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Mol Cell.* **3:**543-553.

Wolfrum C, Asilmaz E, Luca E, Friedman JM, Stoffel M (2004) FoxA2 regulates lipid metabolism and ketogenesis in the liver during fasting and in diabetes *Nature* **432:**1027-10232.

Xie W, Evans RM (2001) Orphan nuclear receptors: the exotics of xenobiotics. *J Biol Chem.* **276:**37739-37742.

Xie W, Barwick JL, Simon CM Pierce AM, Safe S, Blumberg B, Guzelian PS, Evans RM (2000) Reciprocal activation of xenobiotic response genes by nuclear receptors SXR/PXR and CAR. *Genes Dev.* **14:**3014-3023.

Zhou C, Tabb MM, Nelson EL, et al., (2006) Mutual repression between steroid and xenobiotic receptor and NF-kappaB signaling pathways link xenobiotic metabolism and inflammation. *J Clin Invest.* **116:**2280-2289.

Zhou C, Verma S, Blumberg B (2009) The steroid and xenobiotic receptor (SXR), beyond xenobiotic metabolism. *Nucl Recept Signal.* **7:** e00