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Review

Nuclear receptor PXR, transcriptional circuits and metabolic relevance☆,☆☆

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ABSTRACT

The pregnane X receptor (PXR, NR1I2) is a ligand activated transcription factor that belongs to the nuclear hormone receptor (NR) superfamily. PXR is highly expressed in the liver and intestine, but low levels of expression have also been found in many other tissues. PXR plays an integral role in xenobiotic and endobiotic metabolism by regulating the expression of drug-metabolizing enzymes and transporters, as well as genes implicated in the metabolism of endobiotics. PXR exerts its transcriptional regulation by binding to its DNA response elements as a heterodimer with the retinoid X receptor (RXR) and recruitment of a host of coactivators. The biological and physiological implications of PXR activation are broad, ranging from drug metabolism and drug–drug interactions to the homeostasis of numerous endobiotics, such as glucose, lipids, steroids, bile acids, bilirubin, retinoic acid, and bone minerals. The purpose of this article is to provide an overview on the transcriptional circuits and metabolic relevance controlled by PXR. This article is part of a Special Issue entitled: Translating Nuclear Receptors from Health to Disease.

1. Introduction

1.1. Discovery of PXR

The pregnane X receptor (PXR, NR1I2) belongs to the nuclear hormone receptor (NR) superfamily of ligand activated transcription factors [1]. PXR has been shown to play an essential role in xenobiotic metabolism in humans, mice, rats, and rabbits [2–5]. Subsequent studies have strongly suggested that PXR also plays an important role in endobiotic metabolism in humans, mice, and rats [6–16]. The mouse PXR (mPXR) was first discovered and cloned in 1998 based on sequence homology with other NRs and was found to be activated by a variety of compounds, including natural and synthetic glucocorticoids, steroids, pregnane derivatives, antiglucocorticoids, macrocyclic antibiotics, antifungals, and herbal extracts [1,3,17–21]. The human PXR (hPXR) ortholog was subsequently reported as the steroid and xenobiotic receptor (SXR) and pregnane activated receptor (PAR), both exhibiting structural features and activation patterns similar to mPXR [19,20]. SXR/PAR was later confirmed to be orthologous to mPXR by Xie and colleagues via the gene replacement experiment with the PXR knockout mice [22]. PXR has since been cloned from a wide array of species, including mammals, birds, and fish [3,18–21,23–25].

The structural organization of PXR follows that of a typical NR which includes an NH_2 - terminal ligand independent activation function domain (AF-1, A/B region), a highly conserved DNA binding domain (DBD, C region), a less conserved hinge domain (D region), followed by a C-terminal ligand binding domain (LBD, E region) and an activation function 2 domain (AF-2, F region) [26–30].

1.2. PXR's mode of action

When bound to and activated by ligands, PXR translocates from the cytoplasm to the nucleus of the cells [31]. PXR then binds to its DNA response elements as a heterodimer with the retinoid X receptor (RXR). PXR is also capable of recruiting a host of coactivators which includes members of the p160 family of coactivators such as steroid receptor coactivators 1 (SRC-1), TIF/GRIP (SRC-2), and peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α) [32–34]. The DBD of PXR facilitates DNA binding specificity via two highly conserved zinc finger motifs as well as a P-Box motif and D-Box motif which allow the receptor to target and bind its xenobiotic response elements (XREs) located in the 5′ promoter region of PXR target genes [35]. PXR can bind to a variety of DNA response elements containing two copies of the half site consensus sequence AG(G/T)TCA with various spacing, which includes direct repeats DR-3, DR-4, and DR-5, and everted repeats ER-6 and ER-8 [28].

Abbreviations: CYP, cytochrome P450; DDI, drug–drug interaction; G6Pase, glucose-6-phosphatase; GST, glutathione *S*-transferase; NR, nuclear receptor; PCN, prenenolone-16α-carbonitrile; PEPCK, phosphoenolpyruvate carboxykinase; PXR, pregnane X receptor; RIF, rifampicin; SULT, sulfotransferase; UGT, UDP-glucuronosyl transferase; XRE, xenobiotic response element

☆ Mitochondria and Cardioprotection

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2. PXR in xenobiotic metabolism

2.1. Regulation of Phase I enzymes

Functional characterization of PXR has shown that this receptor acts as a xenosensor, playing a major role in protecting organisms from exogenous chemical insults. PXR is highly expressed in the liver, intestine, and kidneys, but low levels have also been found in the peripheral blood monocytes, blood brain barrier, uterus, ovary, placenta, breast, osteoclasts, heart, adrenal glands, bone marrow, and specific brain regions of various species [23,36–40]. Given such a broad range of expression pattern, PXR is well suited to accommodate its metabolic role through the induction of metabolizing/detoxifying enzymes and transporters.

The metabolism of exogenous and endogenous compounds is quintessential for normal physiological functioning of any living organism. PXR is capable of modulating this process through induction of the major Phase I cytochromes P450 enzymes (CYPs). CYPs are a superfamily of heme-dependent monooxygenases, which catalyze the first step of detoxification of aliphatic or lipophillic compounds [41,42]. Highly expressed in the liver and intestine [41], CYPS use hydroxylation and/or oxidation reactions to convert target compounds into more soluble derivatives that are easier to excrete from the body [42]. Activation of PXR has been shown to lead to the transcription of a host of CYP genes in humans and rodents, including CYP3A4, CYP3A23, CYP3a11, CYP2B6, Cyp2b9, Cyp2c55, CYP2C8, CYP2C9, CYP2C19, and CYP1A [18,37,43–47].

It is apparent that since PXR controls the transcription of an array of CYPs, this receptor must be activated by a commensurate number of xenobiotic compounds. This is in fact the case: hPXR has been shown to be activated by a plethora of pharmaceutical drugs that include rifampicin (RIF), rifaximin [48], clotrimazole [3], dexamethasone [18], lovastatin [18] and metyrapone [49] to name a few. PXR is also activated by a variety of environmental pollutants such as 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), di-*n*-butyl phthalate (DBP), chlordane, dieldrin, and endosulfan [50–52]. Finally, PXR can be activated by a variety of medicinal compounds derived from herbal sources including *Schisandra chinensis* (anti-perspiration), *Piper methysticum* (chloraseptic), and *Agauria salicifolia* (arrhythmia) [53].

The ligand-dependent PXR activation has been shown to be species specific at times. For example, in humans and rabbits the antibiotic RIF is a potent PXR activator. However, the same drug has little effect on the mouse or rat PXR. In contrast, the synthetic antiglucocorticoid pregnenolone-16α-carbonitrile (PCN) can activate the mouse and rat PXR but has no effect on hPXR. These species–species differences represent a challenge for pharmaceutical companies attempting to select appropriate animal models to evaluate candidate drugs. The same notion has also led to the initial creation and characterization of the hPXR humanized mice [22].

2.2. Regulation of Phase II enzymes

PXR also can regulate the expression of Phase II drug-metabolizing enzymes, including UDP-glucuronosyl transferase (UGT), sulfotransferase (SULT) and glutathione *S*-transferase (GST) enzymes [54]. Phase II metabolic transformations are often, but do not have to be, preceded by Phase I oxidation reactions which expose or add sites that are ideal for Phase II conjugates. The Phase II metabolic enzymes add polar molecules onto xenobiotics and endobiotics, producing water-soluble, non-toxic metabolites amenable to biliary and/or urinary excretion [55]. Indeed, a major consequence of PXR-mediated Phase II metabolic enzyme regulation is the metabolism and detoxification of bile acids, estrogens, thyroxin, xenobiotics, and carcinogens [56].

UGTs are central Phase II metabolic enzymes which often have distinct as well as overlapping substrates [57]. In humans, 19 enzymes exist which contribute extensively to metabolism by catalyzing the addition of a UDP-glucuronic acid to endo- and xenobiotics, enhancing their water solubility and elimination [57,58]. PXR activation by carbamazepin, RIF, dexamethasone and phenytoin has been linked to the transcriptional activation of several UGTs, including UGT1A1, UGT1A6, UGT1A3 and UGT1A4 [56,57,59,60]. These UGT isoforms are also responsible for the metabolism of a plethora of other drugs such as lamotrigine, olanzapine, retigabine, irinotecan/SN38, acetaminophen, cyproheptadine, nicotine and imipramine, as well as carcinogens such as 4-nitrophenol and 4-OH-PhIP, benzo[a]pyrene [56,57,61,62].

SULT enzyme activities represent another important Phase II pathway of metabolism. SULTs facilitate xenobiotic metabolism by catalyzing the addition of sulfate conjugates on drug molecules leading to more water soluble compounds [63]. In mice, PXR activation by PCN has been shown to upregulate the transcription of several SULT isoforms including Sult1a1, Sult2a1, and Sult5a1 [64]. The role of PXR in human regulation of SULTs in response to xenobiotics is loosely established. Treatment with dexamethasone has been shown to upregulate SULT2A1 in human liver cells, but rifampicin treatment has been shown to have both inductive and suppressive effects [65–67].

GSTs are also major enzymes in Phase II metabolism, as well as many other cytoprotective pathways. GSTs protect cells, organelles, and macromolecules from chemical and oxidative stress, and electrophiles. GSTs catalyze nucleophilic attack via reduced glutathione (GSH) on non-polar compounds containing an electrophilic carbon, rendering them less reactive and more hydrophilic [68,69]. In mice, PXR activation by spironolactone, dexamethasone, and PCN has been shown to induce several GSTs including Gsta3, Gstm1, Gstm2, Gstm3, Gstm4, and MGst1 [69]. The effect of genetic activation of PXR on GST expression in transgenic mice has been shown to be GST isoform-, gender-, and tissue-specific. Human PXR has not been extensively shown to induce GSTs; however, a recent report by Naspinski and colleagues correlated PXR activation by benzo[a]pyrene with subsequent upregulation of several GSTs including GSTA1, GSTA2 and GSTM1 [70].

2.3. Regulation of drug transporters

Drug disposition and metabolism are also regulated by an array of cellular uptake and efflux transporters that control intestinal and hepatic absorption, renal re-absorption, and biliary/urinary elimination. These transporters work in concert with Phase I and II enzymes. The major xenobiotic transporters subject to PXR regulation include the ATP binding cassette family (ABC) proteins expressed in hepatocytes, enterocytes, kidney, and blood brain barrier that regulate cellular export of drugs. Examples of PXR target ABC transporters include the multidrug resistance 1 or P-glycoprotein (MDR1/P-gp), multidrug resistance associated proteins (MRP2, MRP3, MRP4, and MRP5), and breast cancer resistance protein (BCRP) [71–74]. The organic anion transporting polypeptide family (SLC/OATP), which regulates drug and endobiotic influx/uptake into the liver, is also regulated by PXR [75]. The known PXR target SLC/OATP genes include SLCO1A2/OATP1A2, SLCO1B1/OATP1B1, and SLCO1B3/OATP1B3. Finally, the organic ion transporter family, particularly the organic cation transporter SLC22A5/OCTN2, is proposed to have moderate PXR related regulation [76].

2.4. Implication of PXR in drug–drug interactions (DDIs)

As previously discussed, CYPs play an integral role in Phase I metabolism. Among CYP isoforms, the CYP3A subfamily is the most abundant in the liver and also conveys broad substrate specificity [77]. In fact, CYP3As have been shown to be responsible for the metabolism of over 50% of pharmaceuticals on the market today [77]. PXR has been shown to be a major transcriptional regulator of CYP3As, and because of this, it became increasingly apparent that the PXR-mediated regulation of drug-metabolizing enzymes could be involved in clinical DDIs. Such interactions occur when one drug accelerates the