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REVIEW ARTICLE

Functions of pregnane X receptor in self-detoxification

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Abstract Pregnane X receptor (PXR, NR1I2), a member of the nuclear receptor superfamily, is a crucial regulator of nutrient metabolism and metabolic detoxification such as metabolic syndrome, xenobiotic metabolism, inflammatory responses, glucose, cholesterol and lipid metabolism, and endocrine homeostasis. Notably, much experimental and clinical evidence show that PXR senses xenobiotics and triggers the detoxification response to prevent diseases such as diabetes, obesity, intestinal inflammatory diseases and liver fibrosis. In this review we summarize recent advances on remarkable metabolic and regulatory versatility of PXR, and we emphasizes its role and potential implication as an effective modulator of self-detoxification in animals and humans.

Keywords PXR · Inflammatory response · Self-detoxification · CYP450 · NF-κB

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Introduction

Pregnane X receptor (PXR; NR1I2) is a member of the nuclear receptor superfamily and has been valued primarily as a crucial regulator of nutrient homeostasis and drug metabolic detoxification both at the cellular and whole organism level (Cheng et al. 2012; Ma et al. 2015). It is well-established that PXR as a xenobiotic sensor could structurally bind diverse chemicals, including clinical drugs, phytochemicals, dietary constituents, and endogenous substances (Dussault and Forman 2002; Jones et al. 2002; Zhao et al. 2016). Previous studies have revealed that PXR is best characterized for its ability to modulate drug transport and metabolism through the regulation of the target genes that are responsible for the transport and conversion of chemicals (Beigneux et al. 2002; Gao and Xie 2010b). Recent studies have provided new insight into the role of PXR in self-detoxification in response to several inflammatory diseases and endogenous or exogenous toxication (Austin et al. 2015; Azuma et al. 2015). Moreover, PXR as an initiator of alexipharmic signaling, plays a

vital role in the maintenance of intestinal and hepatic health (Cheng et al. 2012). Although the remarkable metabolic and regulatory versatility of PXR has been declared, it is just the beginning to understand the regulatory effect of PXR as an effective modulator of self-detoxification in animals and humans.

PXR, a xenobiotic sensor and effector

Nuclear receptors are members of a superfamily of ligand-inducible transcription factors that mediate specific targets involved in metabolism, development, reproduction and other physiological processes in animals and humans (Blumberg et al. 1998). PXR, one of ligand-inducible transcription factors, is prominently expressed in hepatocytes and gut epithelium. The ligand (such as rifampicin, rifaximin, dexamethasone) binding domain of PXR has been shown to bind structurally diverse xenobiotics. Upon ligand binding, PXR forms a heterodimer with the retinoid X receptor (RXR) (Kliewer et al. 2002) and then the regulatory regions of PXR binds to the promoter of its target genes to regulate their expression (Chen 2008). Moreover, ligand binding to PXR recruits coactivators (i.e., bile acids, possibly other indirect activators such as amino acids, natural products) to activate the expression of target genes encode proteins (such as drug-metabolizing enzymes, immunoprotein and transporters) involved in xenobiotic detoxification and metabolism (Cecchin et al. 2016). PXR was also known as a steroid and xenobiotic sensor (Ma et al. 2015). It was originally identified in mice and shown to be activated by naturally occurring steroids such as pregnenolone and progesterone, as well as synthetic glucocorticoid agonists and antagonists (Blumberg et al. 1998; Li et al. 2012). In addition, PXR is an essential component of the body's self-detoxification system that helps to eliminate xenobiotic and endobiotic substances such as bile acids and their precursors (Johnson et al. 2006; Sonoda et al. 2003).

Modification of PXR protein

PXR is subjected to post-translational modifications which are important for the regulatory effects of PXR on xenobiotic metabolism (Smutny et al. 2013). These post-translational modifications include phosphorylation, SUMOylation, ubiquitination and acetylation (Fig. 1).

Firstly, it is well-known that phosphorylation modulates the activities of PXR (Fig. 1). It has also been shown that various kinases, including p70S6K (Pondugula et al. 2009a), PKA (Ding and Staudinger 2005a), PKC (Ding and Staudinger 2005b), Cdk1/2 (Lichti-Kaiser et al. 2009), can phosphorylate and regulate PXR transcriptional activity (Smutny et al. 2013). However, it is not clear whether phosphorylation at various sites of PXR protein has any physiological significance in vivo, and future studies are needed to be done.

Secondly, regulatory mechanisms of PXR and PXR-mediated pathways involved in the ubiquitination and degradation have been investigated. Masuyama et al. firstly studied the connections between PXR and proteasome signaling using the yeast two-hybrid system (Masuyama et al. 2000). They found that progesterone-occupied PXR interacted with suppressor for gal 1 and then repressed ubiquitylation of PXR and the activity of NF-κB pathway, thereby inducing the inflammatory responses and activating cAMP-dependent protein kinase signaling. Moreover, an E3 ubiquitin ligase, (RING-B-box-Coiled-coil) protein interacting with PKC-1 (RBCC), is identified as a PXR-interacting protein and targets PXR for degradation by the ubiquitin–proteasome pathway (Rana et al. 2013). Moreover, heme-oxidized IRP2 ubiquitin ligase-1 (HOIL-1) could also regulate proteasomal degradation and immune responses through mediating PXR ubiquitination (Elton et al. 2015).

Furthermore, four potential sites with PXR for SUMOylation within PXR have been identified by bioinformatic analysis (Priyanka et al. 2016), and they have been confirmed to be a substrate for SUMOylation in an in vitro approach (Hu et al. 2010). There is also evidence that PXR is SUMOylated in vivo by SUMO-3 after the induction of tumor necrosis factor-α (TNF-α) in hepatocytes, leading to a PXR-mediated repression of NF-κB target gene expression (Treuter and Venteclef 2011). Tan et al.(2016) reports that SUMOylation of PXR exerts suppressive effect on rifampicin-induced expression and activity of cytochrome P450 3A4 (CYP3A4) and P-gp, suggesting that alteration in the SUMOylation status of PXR affects the CYP3A4-mediated drug metabolism and P-gp-regulated drug transport (Tan et al. 2016).

In addition, recent studies have focused on the role of acetylation in the regulation of PXR signaling pathway (Biswas et al. 2011; Staudinger et al. 2011). It has been demonstrated that PXR is acetylated in vivo and the rifampicin-mediated activation of PXR leads to its deacetylation. Some report indicates that the histone deacetylase Sirtuin 1 (SIRT1) is associated with PXR and is partially involved in PXR deacetylation (Buler et al. 2011). Other reports have suggested that peroxisome proliferator-activated receptor γ coactivator 1 alpha (PGC-1α)-mediated PXR may regulate AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways (Dong et al. 2016; Wada et al. 2009).

Collectively, the mutually competitive modifications of PXR protein are complicated and may involve multiple mechanisms. It has been suggested that phosphorylation

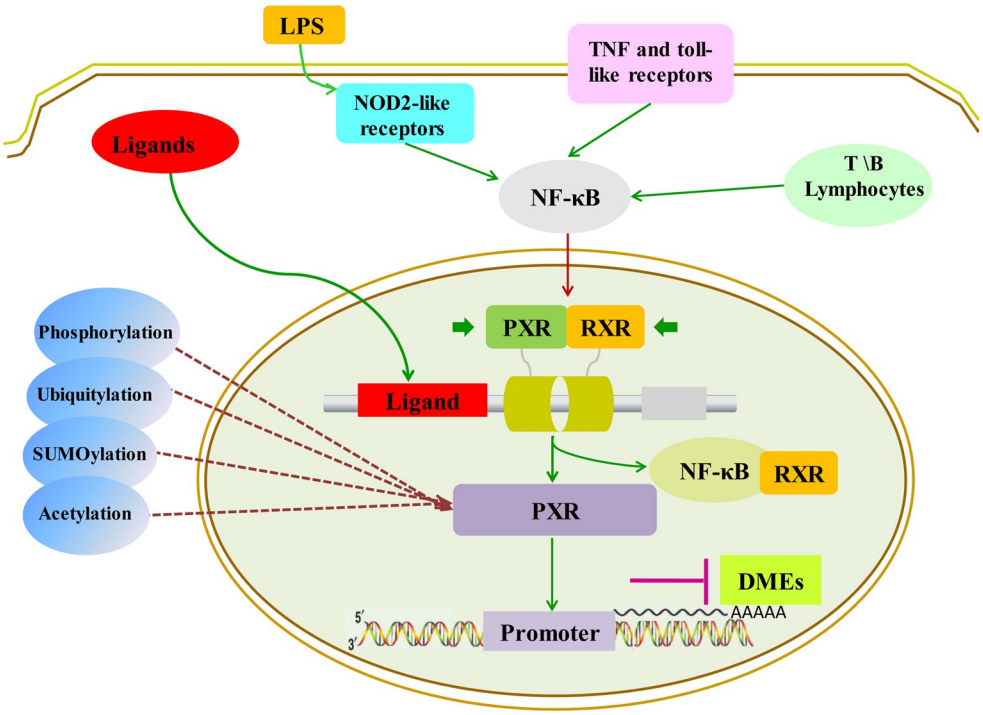

Fig. 1 The crosstalks between PXR and NF-κB through PXR ubiquitylation, phosphorylation, SUMOylation, and acetylation. Lipopolysaccharide, TNF-α or other stimulating factors are used to activate the expression/activity of NF-κB pathway by germline-encoded pattern recognition receptor (including TLR/NOD2) activation, which will lead to the modification of PXR. Firstly, some drug or natural products (e.g., rifampicin, dexamethasone, amino acids) activate the activity of PXR, the activated PXR should bind to its ligands [i.e., retinoid X receptor (RXR)], and then form PXR–RXR heterodimer. Secondly, the regulatory regions of PXR binds to the promoter of its target genes to regulate their expression, at this time, nuclear NF-κB will combine RXR to form NF-κB–RXR compound in the nuclear, thereby decreasing the inflammatory response. Finally, ligand binding to PXR recruits coactivators to activate the expression of target genes [such as drug-metabolizing enzymes (DMEs), immunoprotein and transporters] that encode proteins involved in xenobiotic detoxification. And the process affects ubiquitylation, phosphorylation, SUMOylation, and acetylation of PXR. In addition, PXR can also affect T/B lymphocyte proliferation by decreasing the phosphorylation of NF-κB and human T lymphocytes

may initiate either a positive or negative regulatory signal that directs PXR to SUMOylation, ubiquitination or acetylation (Pondugula et al. 2009b). However, it is not well-known whether the phosphorylation of PXR can directly regulate its self modification.

Function of PXR in metabolism and diseases

Although PXR was initially considered as a xenobiotic sensing nuclear receptor, it is evident that PXR also plays a key role in regulating metabolism (Gu et al. 2006), inflammatory response (Zhou et al. 2006), cell proliferation (Igarashi et al. 2007), glucose, cholesterol and fat metabolism (Buler et al. 2012), endocrine homeostasis (Zhai et al. 2007), and other processes (Gao and Xie 2010) (Fig. 2). Importantly, PXR serves as a self antidotal sensor

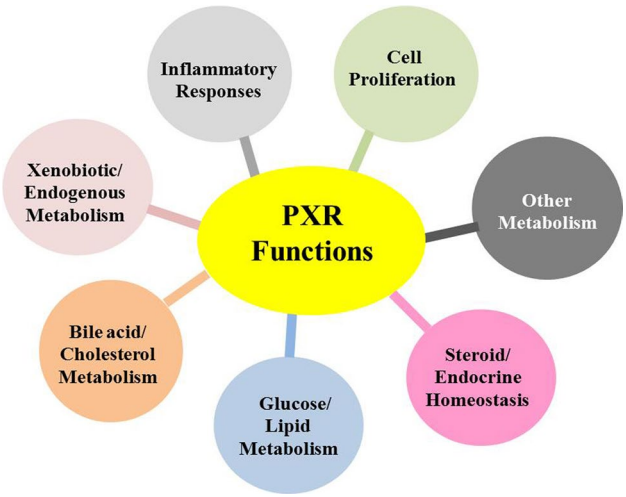

Fig. 2 Functions of PXR in different kinds of metabolism

(Staudinger et al. 2001), and involves in various signaling pathways (i.e., MAPK-ERK, Nrf2/Keap1) (Wada et al. 2009), and regulates the coordinated expression of target genes in metabolic syndrome (Kodama et al. 2007).

Notably, PXR is shown to regulate energy metabolism. Spruiell et al. (2014) explored the function of PXR gene in obesity. They found that PXR played different roles in obesity and glucose homeostasis in hPXR transgenic, and PXR-knock-out (PXR-KO) mice (Spruiell et al. 2014). Specifically, PXR elevated energy metabolism and glucose levels, but severely impaired glucose tolerance. Buler et al. (2011) found that energy state modulated PXR and PXR-mediated pathways and two major regulators (PGC-1a and SIRT1) modulated hepatic energy homeostasis through the activation of PXR pathway (Buler et al. 2011, 2012). Hukkanen et al. (2014) hypothesized that not only did PXR regulate glucose and hepatic lipid metabolism, but also there was a connection between PXR agonists and diabetes susceptibility (Hukkanen et al. 2014). Wahlang et al. (2016) demonstrated that PXR and constitutive androstane receptor (CAR) jointly regulated inflammation responses and energy metabolism in polychlorinated biphenyls (PCB)-mediated non-alcoholic-steatohepatitis (Wahlang et al. 2016).

These findings support the notion that PXR plays an important role in metabolic syndrome and suggest that the PXR activators and antagonists might be potential for the prevention of metabolic diseases. Some reports suggest that ligand-activated PXR repressed key transcription factors and coactivators, that control gluconeogenesis, fatty acid oxidation, cholesterol and ketogenesis through the interactions of protein–protein and drug–drug (Schupp and Lazar 2010; Stedman et al. 2005; Wada et al. 2009). Zhai et al. (2007) found hypertrophy of the adrenal cortex and loss of glucocorticoid circadian rhythm in the PXR activated transgenic mice. These transgenic mice exhibited normal pituitary secretion of adrenocorticotropic hormone and an intact-corticosterone-suppressing effect of dexamethasone, suggesting the presence of a functional hypothalamus–pituitary–adrenal axis (He et al. 2011; Zhou et al. 2006). Thus, PXR might also be a potential endocrine-disrupting factor that plays roles in steroid homeostasis and drug-hormone interactions.

Moreover, evidence of the clinical relevance of PXR expression continues to emerge and suggests that PXR is highly expressed in certain cancers, where it promotes cell proliferation and chemoresistance (Chen et al. 2007; Gupta et al. 2008). Additionally, rifamycin-mediated PXR activation may affect the outcome of tuberculosis therapy (Shehu et al. 2016). Since PXR involves in numerous signaling pathways to maintain cellular and whole body homeostasis, targeting PXR is a promising subject of study in medicine and nutrition. However, when PXR severs as a drug target, especially in cancer therapy, the activation of PXR can induce drug resistance because of its self detoxification function (Cecchin et al. 2016; Robbins and Chen 2014). It is important to note that nutritional regulation and medical therapy are mutually interconnected, so further analysis is warranted to obtain more evidence regarding the purpose of nutritional regulation and drug control in relation to PXR pathway and their interplay.

Functions of PXR in self-detoxification

Role of PXR in self-detoxification

When exogenous and endogenous toxins infect our body, self-detoxification system will make the corresponding change to self-regulate our own status, which is called "self-detoxification" (Cantwell and McBride 1998). Numerous studies demonstrated that the chemical defense conferred by xenobiotic receptor-regulated detoxification and the biological defense involved in self-detoxification are two indispensable functions that provide an organism with survival advantages (Ma et al. 2015). To date, increasing attention is being paid to the mechanisms of PXR on the regulation of self-detoxification (Li et al. 2012). Some studies suggest that PXR interacts with NF-κB pathway in response to xenobiotics (Cheng et al. 2012). Other reports demonstrate that PXR play a protective role in chronic or acute liver diseases by regulating CYP450 (Haughton et al. 2006). Moreover, these two pathways were suggested to interact with each other when they mediated the effects of PXR.

Recent data have given rise to a hypothesis of bidirectional negative crosstalk between PXR and NF-κB pathways, which can also establish a connection between inflammatory response and self-detoxification (Fig. 3). Previous studies reported that the activation of PXR attenuated NF-κB signals, leading to the lower expression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, and TGF-β) (Zhou et al. 2006). Some reports also indicated that PXR silenced by siRNA completely abrogated these anti-inflammatory effects of rifaximin, due to the reduced binding of NF-κB to PXR. Gu et al. (2006) showed that the p65 subunit of NF-κB interacted with PXR and RXR, which prevented the binding of PXR to the promoters of target genes. Thus, the decreased PXR activity increased the susceptibility to inflammatory response (Kubota et al. 2015). Recent studies demonstrated that the PXR-mediated induction of CYP450 enhanced APAP-induced acute liver disease by generating toxic metabolites (Li et al. 2012). Notably, one of the most important responses following self-detoxification reaction is the rapid transcription of CYP450 genes. Once activated, PXR regulates the

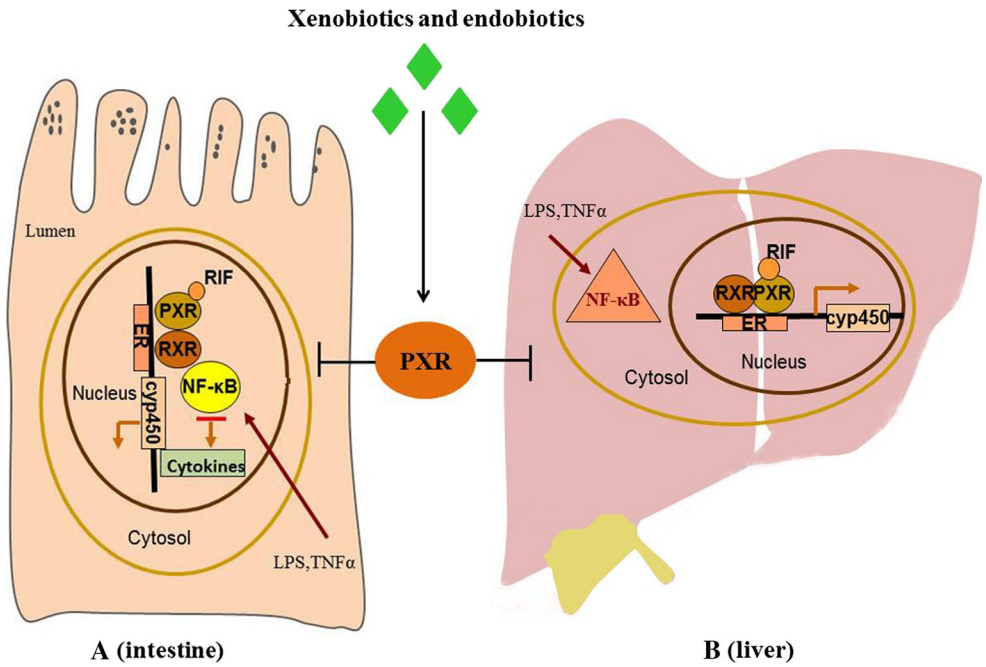

Fig. 3 The regulation of PXR in intestine and liver detoxification and inflammation. Lipopolysaccharide (LPS)-induced intestinal inflammation or liver injury destroys the structure and function of normal cells and has an effect on the expression of drug-metabolizing enzymes (e.g., CYP3A, CYP2B, CYP2C) in self-detoxification system and key genes involved in NF-κB pathway, thereby triggering PXR signaling pathway. This can be ascribed in part to PXR activation improves the activity of CYP450 and the suppression of NF-κB-mediated inflammatory pathway. In intestine (**a**), rifaximin-induced PXR activation in intestinal epithelial cells represses the NF-κB signaling cascade, and then regulates cytokine production (e.g. TNF-α, IL-1β, IL-6, TGF-β), which is associated with suppression of intestinal permeability through PXR activation. Thus, this restores the balance between the intestinal epithelial barrier and immune system, resulting in the reconstruction of cell structure and function. In liver (**b**), rifaximin-induced PXR activation in hepatocyte initially promotes the interactions between NF-κB and RXR, and then increases the transcription of CYP450, this is because p65 as a subunit of NF-κB components, can directly bind RXR. And then this binding could also interfere with the formation of pro-inflammatory cytokines and increase the expression of drug-metabolizing enzymes, and subsequent DNA binding and other favorable signaling pathway activating

transcription of its up- and downstream genes, of which there are some response elements within the promoters (Kast et al. 2002), that encode drug metabolizing enzymes (e.g., SULT, UGT), drug transporter proteins (e.g., MRP2, MDR1, P-gp), and enzymes involved in drug metabolism (e.g., CYP3As, CYP2Bs, CYP2Cs) (Dixit et al. 2016; Skowronek et al. 2016; Ye et al. 2016).

Implication of PXR in intestinal detoxification

It is well-known that PXR is regarded as a target for the treatment of intestinal inflammatory diseases (IBD) and the beneficial effects of PXR activation was partly due to the inhibition of NF-κB pathway (Cheng et al. 2012) (Fig. 3a). Shah et al. found that PXR agonist pregnenolone-16α-carbonitrile decreased the severity of IBD and mRNA expression of several NF-κB target genes in a PXR-dependent manner using PXR-null mice model (Shah et al. 2007). Bioactive component such as notoginsenoside R1 and isorhamnetin extracted from natural plant were also proved to ameliorate IBD via PXR-mediated down-regulation of NF-κB signaling (Dou et al. 2014). These two natural bioactive component both could decrease the production of cytokines, the expression of pro-inflammatory genes, and the phosphorylation of IκB kinase, IκBα, and p65 in the colon in dextran sulfate sodium and trinitrobenzene sulfonic acid-induced colitis in mice via the activation of intestinal PXR pathway (Zhang et al. 2015). Moreover, TLR4/MyD88 was also supposed to help NF-κB signaling mediate the effects of PXR activation (Esposito et al. 2016). Another bioactive component [epigallocatechin gallate (EGCG)] of green tea polyphenol activated PXR and in turn decrease expression of cytochrome P450 3A, in which lithocholic acid produced by bacteria in the colon played an important role (Ikarashi et al. 2017). In addition, other mechanism of PXR signaling in IBD was also demonstrated. Gary et al. found that activation of the PXR protected the intestinal barrier and triggered zonula occludens-1 relocalization during inflammation by modulating cytokine-induced expression of myosin light-chain kinase (MLCK) and JNK1/2 activation (Garg et al. 2016). Since bile acid malabsorption is an important marker of

Crohn's disease and bile acids are potential activators of PXR, the relationship between bile acid malabsorption and PXR pathway were studied. They found that the degree of bile acid malabsorption was closely related to the deactivation of PXR and CYP3A4 a well-characterized target gene of PXR (Iwamoto et al. 2013), which indicated that PXR signaling pathway plays an important role in Crohn's disease. Except that PXR mediates the protective effects against IBD, it was also involved in intestinal epithelial wound healing, because stimulation of the PXR by rifaximin, rifampicin and SR12813 increased cell migration and proliferation which are both critical process of wound healing (Terc et al. 2014).

Implication of PXR in liver detoxification

PXR as a xenobiotic sensor could trigger self-detoxification system in the liver (Wallace et al. 2010) and the mechanism is shown in Fig. 3. Notably, many studies further emphasizes its key role in xenobiotic metabolism as they found that PXR was activated in liver injury (Zeng et al. 2016; Zhou et al. 2016). In primary human hepatocytes, PXR activated by rifampicin inhibited CYP3A4 and P-gp activity in the drug clearance (Holmstock et al. 2013). Clotrimazole as a PXR activator has shown to have a protective effect in an ischemia–reperfusion model in rats (Orr et al. 2004). Furthermore, since PXR ligand activators are antifibrogenic in human liver myofibroblasts in vitro (Fuchs et al. 2016) and in vivo animal models of liver fibrosis (Cave et al. 2016). PXR activators may be better drugs for the treatment of liver fibrosis than other non-PXR-activating drugs (Wallace et al. 2010). Recently, acetylated deoxycholic (DCA) and cholic acids (CA) were proved to be potent ligands of PXR and they induced mRNA expression of PXR-target genes such as CYP3A4, CYP2B6 and ABCB1/MDR1 (Carazo et al. 2017). These results suggested that endogenous ligands might have the potential to be a safe therapy in inflammatory and other liver diseases and further confirmed the involvement of PXR in hepatic detoxification system.

A previous study demonstrated that the anti-inflammatory actions of PXR agonists such as cyclosporine A are mediated by the inhibition of NF-κB activity (Harvey et al. 2000). In a recent study, Ye et al. (2016) examined the effect of PXR on tetrachloromethane (CCl4)-induced mouse liver disease. Their results indicated that anti-inflammatory effect of PXR activated by ginkgolide A might be mediated by the enhanced transcription level of I kappa B alpha (Ye et al. 2016). These observations may be important for clinical therapy, because some liver disease patients can availably take PXR activators for prolonged periods, especially, primary biliary cirrhosis patients (Chiang et al. 2014; Schmuth et al. 2014; Xie et al. 2016). Additionally, the marked increase in hepatic CYP3A11 and MRP3/4 expression in a bile duct ligation model of cholestasis in mice suggests that PXR plays a protective role in cholestatic patients by increasing the hydroxylation and efflux of toxic bile acids from hepatocytes into blood, through its regulation of multiple self detoxification (Noll et al. 2016). Thus, PXR is considered to be a self-detoxification sensor, which may offer hope for the development of new therapies for liver diseases.

Interactions of PXR in intestine and liver detoxification

Currently, many researchers have gradually focused their attention on a correlation between metabolic and molecular expression, which links the gut-liver axis to the occurrence of self-detoxification (Cecchin et al. 2016; Fuchs et al. 2016). It is reported that intestinal bacteria and their products (such as bacterial endotoxin, cytokines, etc.) in intestinal inflammatory diseases could enter the liver through circulation (Taniki et al. 2015), and ultimately resulted in dysfunction of self-detoxification system (Brandl and Schnabl 2015).

Growing evidence suggests that PXR pathway plays a vital role in the maintenance of gut and liver homeostasis through the inhibition of inflammatory response and improvement of self-detoxification. However, it is unclear whether the PXR signaling pathway has different associations with intestine and liver detoxification, and whether these conditions are connected with each other (Staudinger et al. 2013). Our research group has focused on the regulation of PXR activity by nutrients (e.g., alpha-ketoglutarate, amino acids), in order to improve inflammatory response and self-detoxification. To data, He et al. (2017a) found that alpha-ketoglutarate (AKG) had potent effects on regulating the PXR and its downstream targets such as CYP3As and CYP2Bs in vivo and in vitro, although AKG is not a known PXR ligand. One potential mechanism for the up-regulation of the PXR pathway is through the down-regulation of NF-κB pathway which in turn de-represses the PXR-regulated target expression (He et al. 2017b). Other potential mechanism that AKG may be enhance the activity of the AMPK pathway to activate PXR signal (He et al. 2017a).

Future perspectives

PXR is a critical regulator of nutrient metabolism and metabolic detoxification such as xenobiotic metabolism, inflammatory responses, glucose, cholesterol and lipid metabolism, which makes it a potential therapeutic target as many commonly prescribes drug and natural products could activate PXR pathway. Although studies have

showed that post-translational modifications of PXR protein mostly including phosphorylation, SUMOylation, ubiquitination and acetylation are important for the functions of PXR, works still need to be done in order to elucidate the interactions of different post-translational modifications. Since PXR-mediated NF-κB and CYP450 signaling pathways mainly mediated the regulation effects of PXR on self-detoxification in both liver and intestine, the specific crosstalk between intestine and liver self-detoxification mediated by PXR would be an interesting topic for future studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All experimental procedures were approved by the Institutional Animal Care and Use Committee at Institute of Subtropical Agriculture, The Chinese Academy of Sciences.

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