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The Pregnane X Receptor in Tuberculosis Therapeutics

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Abstract

Introduction—Among the infectious diseases, tuberculosis (TB) remains the second cause of death after HIV. TB treatment requires the combination of multiple drugs including the rifamycin class. However, rifamycins are activators of human pregnane X receptor (PXR), a transcription factor that regulates drug metabolism, drug resistance, energy metabolism, and immune response. Rifamycin-mediated PXR activation may affect the outcome of TB therapy.

Areas covered—This review describes the role of PXR in modulating metabolism, efficacy, toxicity, and resistance to anti-TB drugs; as well as polymorphisms of PXR that potentially affect TB susceptibility.

Expert opinion—The wide range of PXR functions aside mediating drug metabolism and toxicity in TB therapy is underappreciated and thus understudied. Further studies are needed to determine the overall impact of PXR activation on the outcome of TB therapy.

Keywords

tuberculosis; therapeutics; pregnane X receptor; metabolism; toxicity

1. Introduction

The pregnane X receptor (PXR) is a ligand dependent transcription factor that belongs to the super family of nuclear receptors [1, 2]. After ligand binding, PXR forms a heterodimer with retinoid X receptor, which together bind to the DNA response element of its target genes to initiate their transcription. The PXR is unique in that it has an indiscriminate ligand-binding domain [1, 3]. Thus, PXR ligands vary widely from prescription drugs to herbs, dietary compounds, steroids, vitamins and environmental compounds/contaminants [1, 4–8]. Species differences of PXR activation have been well-characterized [1, 2, 4]. Like other nuclear receptors, PXR has a conserved DNA binding domain [9]. However, the ligand

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Declaration of interest

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binding domain of PXR differs remarkably amongst species [9, 10], which explains the differences in the activation of PXR and its target genes across species.

The rifamycins are among of the most important classes of drugs in TB therapy and are ligands of human PXR [11–13]. PXR activation modulates drug metabolism, energy metabolism and immune response [2, 4, 14, 15], which can affect the efficacy and safety of TB therapy. In addition, polymorphisms of *PXR* may affect TB susceptibility [16]. In this review, we focus on the potential role of PXR in anti-TB drug metabolism, toxicity, efficacy, resistance, and TB susceptibility.

1.1. Functions of PXR

1.1.1. Regulation of drug metabolizing enzymes and transporters—The fate of drugs is modulated by drug metabolizing enzymes (Phase I and II) and transporters. Phase I drug metabolizing enzymes consists mainly of the cytochrome P450 (CYP) family [17]. They usually catalyze the conversion of parent compounds to more polar molecules through oxidation [17, 18]. Phase II enzymes are made up of transferases that add polar groups like glucuronides to make the parent drug inactive and more water-soluble [18, 19]. Transporters together with phase I and II drug metabolizing enzymes coordinate the process of drug metabolism and disposition [20].

The PXR regulates drug metabolism and excretion through modulating the expression of drug metabolizing enzymes and transporters [1, 20]. The PXR regulates an ample number of the phase I enzymes including CYP3A4, CYP2B6 and CYP2C9 [1, 21–24], which all play an important role in the metabolism of clinically used drugs. The PXR also regulates phase II enzymes and transporters, such as glutathione S-transferase (GST), sulfotransferase 2A1 (SULT2A1), UDP-glucuronosyl transferase 1A1 (UGT1A1), P-glycoprotein, multidrug resistance-associated protein 2 (MRP2), and organic anion transporting polypeptide 2 (OATP2) [25–32]. Therefore, PXR activation significantly affects drug metabolism and disposition [33].

1.1.2. Drug resistance—The human PXR has been implicated in the emergence of resistance to anti-cancer drugs. High expressions of PXR and its target genes CYP3A4 and P-glycoprotein were observed in a prostate cancer cell line that showed resistance to chemotherapy drugs [34]. High expressions of PXR have also been observed in breast cancer, endometrial cancer and colon cancer, which were thought to be important for drug resistance in chemotherapy [35–38].

1.1.3. Energy metabolism—PXR activation suppresses gluconeogenesis through interaction with forkhead box protein O1 (FoxO1), cAMP response element-binding protein (CREB), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α) and hepatocyte nuclear factor 4 α (HNF4 α) [39–41]. In lipid metabolism, PXR activation inhibits fatty acid β -oxidation and ketogenesis through the down regulation of carnitine palmitoyltransferase 1 a (Cpt1a) and 3-hydroxy-3-methylgluturate-CoA synthase 2 (Hmgcs2), the two key enzymes in fatty acid β -oxidation and ketogenesis, respectively [42]. Furthermore, PXR upregulates the expression of stearoyl-CoA desaturase 1 (Scd1), a key

enzyme in the synthesis of unsaturated fatty acids, thus promoting hepatic lipogenesis [43, 44].

1.1.4. Anti-inflammatory effects—Expression of PXR has been detected in immune cells [45]. Interestingly, ligand mediated PXR activation inhibited the proliferation and function of T lymphocytes [15]. Rifampicin (RIF) as a PXR activator has long been known to have immunosuppressive effects [46–48]. NF- κ B is a master regulator of inflammatory and immune responses to infection [49]. PXR activation inhibits the NF- κ B signaling pathways [50]. In a dextran sulphate sodium (DSS)-induced inflammatory bowel disease (IBD) mouse model, mouse Pxr ligand pregnenolone-16 alpha carbonitrile (PCN) attenuated DDS-induced toxicity and inflammation in the colon through the inhibition of NF- κ B [51].

1.2. PXR activation by anti-TB drugs

Rifamycins, including RIF, rifabutin, rifapentine and rifalazil, are an important class of antibiotics used for TB treatment. The rifamycins have variable effects on PXR. RIF was discovered in 1959 and has become the mainstay of TB treatment [52]. RIF is a potent activator of the PXR [1, 2, 4, 14, 53]. RIF via the activation of PXR induces the expression of multiple important metabolizing enzymes [21, 31, 54, 55], thus affecting the pharmacokinetics of a wide variety of clinical drugs. Rifabutin and rifapentine also induce CYP3A4 via the PXR but to a lesser extent compared to RIF [11–13, 56], which reduces their extent of drug-drug interactions. Rifalazil does not induce metabolizing enzymes when compared to RIF and rifabutin, suggesting no effect on PXR [57].

Isoniazid (INH) is a first line agent for TB treatment. INH induces PXR expression in rats [58]. However, the functional relevance of this induction remains to be determined and has not been reported in humans. No evidence has been shown for PXR interaction with other anti-TB drugs, including pyrazinamide, ethambutol, streptomycin, bedaquiline, fluoroquinolones, capreomycin, cycloserine and aminoglycosides.

2.0. PXR on drug metabolism and disposition

For the initial phase of TB therapy, the standard treatment for TB patients includes RIF, INH, pyrazinamide, and either ethambutol or streptomycin [59]. After 2 months of treatment, pyrazinamide plus ethambutol or streptomycin can be stopped; but RIF plus INH needs be continued as daily or intermittent therapy for 4 more months. As mentioned earlier in this review, RIF activates PXR and up regulates the drug metabolizing enzymes and transporters that may affect the metabolism and disposition of co-administered drugs.

2.1. Rifamycin metabolism

Through the PXR, CYP3A4 is highly induced by RIF but to a lesser extent by rifabutin and rifapentine [60, 61]. However, the metabolism of rifamycins seems to be CYP3A4-independent except for rifabutin. Therefore, PXR activation will accelerate rifabutin metabolism through CYP3A4 induction. Interestingly, RIF can accelerate its own metabolism and thus reduces its half-life and plasma concentration [62–64]. This should be PXR-mediated because RIF is a potent PXR activator. However, it remains unknown how PXR modulates RIF metabolism.

2.2. INH metabolism

INH is mainly metabolized by arylamine *N*-acetyltransferase type 2 (NAT2), a highly polymorphic enzyme [65]. However, PXR does not regulate NAT2. INH metabolism through the CYP-dependent pathway to generate isonicotinic acid was observed in the isolated rat hepatocytes pretreated with phenobarbital, 3-methylchlorathene and RIF [66, 67]. However, the individual CYP that contributes to the formation of isonicotinic acid in INH metabolism remains unknown. CYP3A4 has been thought to be involved in metabolism and bioactivation of INH, but the study using *Cyp3a*-null mice dispute these associations [68].

2.3. Metabolism of other anti-TB drugs

Pyrazinamide is metabolized to pyrazinoic acid by a deamidase and to 5-hydroxypyrazinoic acids by xanthine oxidase, xanthine dehydrogenase and aldehyde oxidase [69–72]. All these enzymes involved in pyrazinamide metabolism are not regulated by PXR. Ethambutol is a substrate of P-glycoprotein [73], thus activation of PXR by rifamycins may affect the intracellular levels of ethambutol. The FDA approved bedaquiline for the treatment of multi-drug resistant TB in 2012 [74]. Bedaquiline specifically inhibits the ATP synthase of *Mycobacterium tuberculosis* (Mtb), which depletes ATP in Mtb and leads to Mtb death [75]. Bedaquiline is more effective against the resistant strains of Mtb compared to wild type strains [75]. Bedaquiline is metabolized by CYP3A4 to an *N*-desmethyl metabolite [76, 77]. Therefore, PXR activation and CYP3A4 induction will accelerate bedaquiline elimination. This is supported by a clinical study showing a significant decrease in plasma concentration of bedaquiline when it is co-administered with RIF [78]. Thus bedaquiline cannot be taken together with a PXR activator.

2.4. Metabolism of non-TB drugs

Drug-drug interactions are common during TB therapy especially with RIF-containing regimens [79]. Patient groups particularly at risk of clinically relevant drug interactions include those with comorbid conditions like HIV, transplant patients and the elderly, which present with chronic illnesses like diabetes, hypertension or deterioration of liver and kidney function [79, 80]. All these conditions necessitate use of multiple medications alongside TB therapy, thus increasing the chances of drug-drug interactions.

TB therapy in HIV patients is particularly complicated by drug-drug interactions between the rifamycins and the HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The HIV PIs are substrates of CYP3A4 [81–83]. RIF and rifabutin have been reported to reduce the plasma concentrations of HIV PIs through their ability to induce CYP3A4 [84]. The NNRTIs are quite different in their metabolism on an individual basis. Rifabutin and RIF significantly decrease the steady state plasma concentration of delavirdine in patients receiving RIF plus delavirdine or rifabutin plus delavirdine compared to those receiving delavirdine alone [85, 86]. Thus concomitant administration of delavirdine with either of the rifamycins is not advised. Nevirapine is metabolized by both CYP3A4 and CYP2B6 [87]. Nevirapine plasma concentration declined when co-administered with RIF [88, 89]. Efavirenz is metabolized mainly by CYP2B6, an

enzyme that is upregulated by PXR [55, 90, 91]. However, the data are inconsistent with a clinically significant effect of RIF on efavirenz metabolism [89, 92].

Individuals who undergo any form of transplants are susceptible to TB due to the intake of immunosuppressive medications like cyclosporine and tacrolimus, which are both substrates of CYP3A4 and P-glycoprotein [80, 93–96]. The disposition of cyclosporine and tacrolimus can be affected by PXR ligands like RIF, which makes TB treatment with RIF-containing regimen complex. These interactions have been found in clinical studies where subtherapeutic concentrations of cyclosporine or tacrolimus were observed in transplant patients receiving RIF-containing regimens [80, 97–99]. Reduced therapeutic concentrations can lead to allograft rejection in transplant patients. Therefore, careful monitoring and dose adjustments are important for achieving desired outcome of transplant.

Acetaminophen is an over-the-counter analgesic used in combination with many prescription and non-prescription medications. It is the leading cause of drug-induced liver injury in the United States [100]. Acetaminophen-induced liver injury can be exacerbated by INH and RIF due to induction of CYP2E1 and 3A4, respectively [101, 102]. Therefore, it is of paramount importance for clinicians to monitor and educate TB patients on the risk of such adverse events.

3.0. PXR on the side effects of anti-TB drugs

One of the caveats of TB therapy is the risk of hepatotoxicity. A higher incidence of liver injury in patients has been reported with RIF and INH co-treatment compared to taking either drug alone [103]. The widely held view for RIF and INH-induced liver injury is that RIF as a CYP inducer potentiates INH bioactivation and toxicity [104]. However, no evidence is available to prove the role of CYP in INH metabolism and bioactivation. The formation of anti-INH, anti-CYP2E1, anti-CYP3A4 and anti-CYP2C9 antibodies was shown in patients with INH-induced liver failure but not in patients treated with INH without liver failure [105]. These findings suggest the association of CYP3A4 and 2C9 that are PXR target genes with the metabolism and toxicity of INH.

A mechanism independent of INH metabolism has also been proposed for RIF and INH-induced liver injury [106]. Studies using PXR-humanized (hPXR) mice demonstrated that RIF and INH co-treatment resulted in liver injury by perturbing the heme biosynthesis pathway [106]. In the same study using hPXR mice, treatment with RIF plus acetyl hydrazine or hydrazine, two INH metabolites believed to be responsible for liver injury, did not cause liver damage, suggesting that acetyl hydrazine and hydrazine are not the cause of INH hepatotoxicity. These findings illustrate a new mechanism for RIF and INH-induced liver injury independent of INH metabolism, but dependent on the PXR signaling pathways.

In 2001, the Centers for Disease Control and Prevention (CDC) revised the guidelines for the treatment of patients with latent TB using RIF and pyrazinamide due to the alarming rate of hepatotoxicity [107]. Unfortunately, the mechanism behind this toxicity is still poorly understood. Though RIF was shown to improve the renal excretion of uric acid that causes joint pain in patients receiving pyrazinamide, RIF did not affect the metabolism or excretion

of pyrazinamide [108]. Further studies are needed to investigate whether PXR modulates the hepatotoxicity associated with RIF and pyrazinamide co-treatment.

4.0. PXR on the efficacy of anti-TB drugs

The immune system plays an important role in the containment of TB infection [109]. TB is typified by the formation of granulomas, a collection of macrophages, neutrophils and monocytes formed to restrict bacteria at the site of infection [110, 111]. Inflammation in the lungs during TB infection is important as it modulates the influx of immune cells to the site of infection [112]. These immune cells mediate the killing of Mtb. However, excessive inflammation is detrimental to the host as it promotes TB pathology and tissue destruction [112, 113]. Therefore, the balance in pro-inflammatory vs anti-inflammatory responses is needed to adequately control Mtb infection. Inadequate or excessive inflammation in TB patients can allow progression of disease [114].

Anti-inflammatory agents have been suggested as an adjunct therapy to the current anti-TB regimens [115]. Mtb uses cyclic adenosine monophosphate (cAMP) secreted from macrophages to elicit the production of tumor necrosis factors (TNF)-alpha in the early phase of TB infection, which then promotes lung damage and bacterial survival through granuloma formation [116, 117]. These data provide the rational for use of anti-inflammatory agents in TB therapy. Indeed, the use of steroids in TB therapy showed potential benefit in decreasing mortality [118, 119].

Immunosuppressive effect of RIF has been observed soon after its introduction to the clinic [46, 120, 121]. RIF decreases inflammation through the activation of PXR. For future studies, it will be valuable to explore whether rifamycin-mediated immunosuppression contributes to the efficacy of rifamycins. While the immunosuppressive effects of RIF are of interest, it might be difficult to disentangle these from its antimicrobial activity.

5.0. PXR on TB drug resistance

Drug resistance in TB therapy has become a global issue and is threatening the control of this widespread epidemic [122]. Risk factors associated with the development of TB drug resistance include lack of adherence, inadequate drug concentrations, malnutrition, and co-infection with diseases like HIV [123–125].

Inadequate concentrations of anti-TB drugs at the target site contribute to the development of drug resistance [126–130]. PXR activation may affect systemic pharmacokinetics of multiple anti-TB drugs, such as rifamycins, ethambutol, and bedaquiline. In addition, the expression of PXR and its target genes in the lungs [131], may affect the tissue specific pharmacokinetics of anti-TB drugs at the site of infection. For example, the efflux transporter P-glycoprotein is highly expressed in lung tissues and alveolar macrophages [132, 133], which can therefore affect the disposition of its substrate drugs and contribute to the development of TB drug resistance. Nevertheless, no studies so far have been conducted to determine the effect of PXR on development of TB drug resistance just like it has been shown in cancer chemoresistance [34–38, 134]. Furthermore, PXR potentiates anti-TB drug-mediated hepatotoxicity [106]. Side effects of anti-TB drugs affects the attitudes of patients

towards compliance to their medications and in some cases lead to discontinuation of treatment [135]. With the poor adherence to taking medication or interruption of treatment, the possibility of developing TB drug resistance increases.

In addition to drug levels, the host factors like status of nutrition and immune system may contribute to the development of TB drug resistance [123–125]. It has been well established that host-pathogen interaction at the level of immune system is important in the progression of TB [136]. The activation of PXR by its ligands in TB therapy can lead to the repression of inflammation, which may decrease the host's ability to fight against Mtb. Moreover, PXR disturbs glucose and lipid metabolism [39–44], which may also decrease the host's ability to fight against Mtb. Further studies are needed to determine the impact of PXR-mediated immunosuppression and disturbance of energy metabolism in development of TB drug resistance.

6.0. PXR on TB susceptibility

The facts about TB susceptibility and progression to disease remain enigmatic. People living in high endemic areas have a higher risk of acquiring TB infection, but only about 5% of them who get infected with Mtb progress to clinical disease [137]. The emerging knowledge of PXR provides novel insights into TB susceptibility.

Both PXR and vitamin D receptor (VDR) belong to the nuclear receptor family II (NR1I). The vitamin D and its derivatives through VDR suppress the functional differentiation of dendritic cells, cytotoxic T cells, helper T cells and the production of IFN- γ and IL-12 after Th-1 type stimulation, thus inhibiting Th-1 mediated immune responses [138, 139]. Variants of VDR are associated with TB susceptibility [140]. Likewise, a PXR variant rs3814057 was found to be associated with increased susceptibility to TB. Furthermore, two other PXR SNPs, rs7643645 and rs2461823, in female subjects with genotype AA were associated with increased and decreased risk of hepatotoxicity during TB therapy, respectively [16]. However, it is unclear whether these SNPs of PXR lead to the gain or loss of PXR function.

Subjects with compromised immune system are more susceptible to TB, such as HIV patients or patients with organ transplant receiving immune suppressors. PXR activation has immunosuppressive effects [15]. Unfortunately, PXR activators are very common in daily life, ranging from clinically used drugs, herbs, phytochemicals and phytoestrogens, to environmental contaminants [6, 141]. Further studies are needed to determine the consequence of long-term exposure to PXR activators on the functions of immune system and TB susceptibility.

7.0. Conclusion

The role of PXR in TB therapy seems to be a double-edged sword. The function of PXR in drug metabolism and disposition may negatively impart TB therapy through drug-drug interactions or adverse effects. Conversely, anti-inflammatory effect of PXR may help the host achieve the right balance of inflammation needed at the site of infection. PXR may also be associated with TB drug resistance and TB susceptibility.

8.0. Expert opinion

The role of nuclear receptors in TB pathogenesis is currently emerging as an exciting area of research. The liver X receptor (LXR), peroxisome proliferator-activated receptor gamma (PPAR γ) and the testicular receptor 4 (TR4) are involved in TB pathogenesis due to their functions in modulating immune response [142, 143]. Disruption of the LXR signaling pathways in mice increased their susceptibility and progression to systemic TB infection [142]. Lxr-null mice presented a defect in the early neutrophilic inflammatory response and decreased Th17/Th1 response in the lung. However, prophylactic and therapeutic treatment of wild-type mice with a LXR agonist increased resistance to TB infection and improved inflammatory and Th17/Th1 response [142]. Conversely, the activation of PPAR γ boosts Mtb survival [144]. PPAR γ activation down regulates pro-inflammatory responses and promotes the formation of macrophage foam cells, which provides a niche for Mtb to survive [143, 145].

The nuclear receptor PXR is a key modulator in the triangular interactions amongst anti-TB drugs, Mtb, and host (Figure 1). The class of rifamycins is the backbone in TB therapy, which activates PXR in the host [60, 61, 129]. Activation of PXR up regulates drug metabolizing enzymes and transporters that can affect the systemic and/or tissue specific pharmacokinetics of anti-TB drugs and other co-administered drugs. PXR activation also potentiates side effects of anti-TB drugs [106]. Moreover, PXR activation suppresses immune response in the host [46, 120, 121]. Therefore, PXR activation may affect the outcome of TB therapy through the regulation of drug metabolism and immune response in the host.

Since the nuclear receptors are the at cross roads of regulating inflammation and immunity, research in this field holds promise for exploring nuclear receptors as targets in TB management. Regarding the PXR, no research so far has been conducted to examine its effect on TB pathology and/or therapy. The genetically engineered PXR mouse models may serve as ideal tools to determine the role of PXR in TB pathogenesis and therapeutics. The following questions should be considered to explore the role of PXR in the triangular interactions amongst anti-TB drugs, Mtb, and host: (1) whether PXR activation affects the drug concentrations at the site of Mtb infection? (2) whether PXR-mediated immunosuppression benefits the efficacy of anti-TB drugs? (3) whether PXR-mediated immunosuppression is involved in the development of TB drug resistance? and (4) how PXR polymorphisms are associated with TB susceptibility? Moreover, PXR activation disturbs glucose and lipid metabolism [39, 40, 42]. It is reasonable to question whether PXR affects the outcome of TB therapy through the regulation of energy metabolism, because malnutrition in the host is associated with side effects of anti-TB drugs, drug resistance, and TB susceptibility [124, 125].

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Article highlights box

- Anti-tuberculosis (TB) drugs such as rifamycins activate the Pregnane X Receptor (PXR), a transcription factor that regulates drug metabolism, drug resistance, energy metabolism, and immune response.
- PXR activation may accelerate the elimination of rifamycins, ethambutol, and bedaquiline.
- PXR mediates many interactions between anti-TB drugs and co-administered drugs in TB patients.
- PXR modulates the hepatotoxicity of rifampicin and isoniazid. It remains unknown whether PXR contributes to the hepatotoxicity of other rifampicin-containing anti-TB regimens.
- Moderate immunosuppression mediated by PXR activation may benefit the efficacy of TB therapy.
- Activation of PXR and PXR polymorphisms may contribute to TB drug resistance and TB susceptibility.

Figure 1. The role of PXR in the triangular interactions amongst anti-TB drugs, Mtb, and host Anti-TB drugs like rifamycins activate PXR in the host and potentiate liver injury associated with anti-TB drugs. Activation of PXR in return accelerates the metabolism of some anti-TB drugs. PXR activation also modulates the immune response to Mtb. PXR-mediated regulation of drug metabolism and immune response to Mtb may affect the outcome of TB therapy.