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Pregnane X receptor as a target for treatment of inflammatory bowel disorders

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Abstract

Pregnane X receptor (PXR; NR1I2), a member of the nuclear receptor superfamily, has a major role in the induction of genes involved in drug transport and metabolism. Recent studies in mice have provided insight into a novel function for PXR in inflammatory bowel disease (IBD). The mechanisms of the protective effect of PXR activation on IBD is not fully established, but is due in part to the attenuation of nuclear factor kappa B (NF- κ B) signaling that results in lower expression of proinflammatory cytokines. Recent clinical trials with the antibiotic rifaximin, a PXR agonist in the gastrointestinal system, have revealed its potential therapeutic value in the treatment of intestinal inflammation in humans. Thus, PXR may be a novel target for IBD therapy.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract. IBD has shown a steep rise in incidence and is now one of the five most prevalent gastrointestinal diseases in the USA¹. IBD comprises Crohn's disease (CD) and ulcerative colitis (UC). UC is an inflammatory disease that affects the lining of the colon, whereas CD can affect any part of the digestive tract, with inflammation that extends deeper into the layers of the intestinal wall. While the etiology of IBD is unclear, the prevailing view is that it is triggered by multiple factors, including environment, genetic variations, intestinal microbiota, and disturbances in the innate and adaptive immune response². The most common symptoms of both UC and CD are recurring abdominal pain, diarrhea, rectal bleeding and malnutrition. IBD patients have a much higher incidence of colorectal cancer compared to the general population³. Moreover, IBD can cause other health problems that occur outside the digestive system, notably increased inflammation elsewhere in the body, including the joints, eyes, skin, and liver⁴.

Under normal conditions, the intestinal mucosa is in a state of "controlled" inflammation regulated by a delicate balance between pro-inflammatory and anti-inflammatory cytokines. The pathogenesis of IBD involves defects in the intestinal epithelial barrier and mucosal immune system, resulting in active inflammation and tissue destruction. There is a

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Conflict of Interest:

The authors received rifaximin from Salix Pharmaceuticals, Inc. There are no other conflicts of interest to declare.

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reciprocal crosstalk leading to IBD, with a loss in intestinal epithelial barrier integrity that results in inflammation due to increased diffusion of luminal microbiota. The activation of the mucosal inflammatory response leads to a further compromised intestinal barrier⁵. This cyclical feed-forward mechanism results in chronic inflammation and tissue injury.

Although the primary cause is not completely clear, several risk loci have been identified by genome-wide association studies^{6–8}. These loci map to genes that are involved in key cellular processes such as innate immune recognition⁹, autophagy¹⁰, cell-cell contact¹¹ and aspects of cytokine signaling¹². In addition, certain nuclear receptors^{13–15} are implicated in the etiology of IBD through their roles in controlling the immune responses and hormone-regulated homeostasis.

Nuclear receptors regulate the inflammatory response in several disease states, such as atherosclerosis, obesity and type II diabetes, IBD, Alzheimer's disease, multiple sclerosis, and cancer¹⁶. Growing evidence in humans and animal models revealed that orphan and adopted orphan nuclear receptors, such as peroxisome proliferator-activated receptor (PPAR) α (NR1C1)¹⁷, PPAR β (NR1C2)¹⁸, PPAR γ (NR1C3)¹⁹, glucocorticoid receptor (GR; NR3C1)²⁰, liver X receptor (LXR; NR1H2)²¹, farnesoid X receptor (FXR; NR1H4)¹⁵, vitamin D receptor (VDR; NR1I1)²², RAR-related orphan receptor γ (ROR γ ; NR1F3)²³, hepatocyte nuclear factor 4 α (HNF4 α ; NR2A21)²⁴, estrogen receptor α (ER α ; NR3A1)²⁵, and pregnane X receptor (PXR; NR1I2)²⁶ regulate the inflammatory response in IBD. Among these, PXR is the best characterized for its modulation of drug transport and metabolism through the regulation of target genes responsible for the transport and conversion of chemicals into metabolites that are more easily eliminated from the body²⁷. It is activated by xenobiotics, including many drugs; thus, it contributes to drug metabolism and clearance and is involved in drug-drug interactions. PXR is also emerging as an endobiotic receptor that regulates the inflammatory response²⁸. In this review, we summarize the role of PXR as an effective modulator of IBD and discuss the potential therapeutic application of its ligands in the clinical treatment of IBD.

PXR

PXR is well-known for its pivotal function in the control of drug metabolism²⁷. PXR has a flexible ligand binding pocket²⁹ which can bind structurally diverse ligands, including prescription drugs, natural products, dietary supplements, environmental pollutants, endogenous hormones and bile acids²⁷. Similar to other members of the nuclear receptor superfamily, PXR possesses a conserved *N*-terminal DNA-binding domain (DBD) and *C*-terminal ligand-binding domain (LBD), and functions as a heterodimer with the 9-*cis* retinoic acid receptor, also known as retinoid X receptor α (RXR α ; NR2B1), to control gene transcription³⁰. Although the human and mouse PXR share nearly 80% amino acid identity across the LBD, 96% amino acid identity in the DBD, and display similar tissue expression patterns, the differences between the LBD sequences across species influences species-specific responses to ligand activation. For example, rifampicin has virtually no effect on the mouse PXR at typical pharmacological doses, but is a very potent agonist of the human PXR³¹. Conversely, pregnenolone-16 α -carbonitrile (PCN) only weakly activates the human PXR but is an efficacious agonist of the mouse PXR³². Human PXRs are expressed in small intestine, colon, liver, and gall bladder, with lower expression in stomach³³. The distribution and function of human PXRs in the gastrointestinal system contribute to its emerging role as a modulator of inflammation in the intestinal mucosa barrier.

Role of PXR in the pathogenesis of IBD

PXR agonists in the treatment of IBD

A role for PXR in protection against IBD was revealed by studies using an experimentally-induced IBD model with a PXR agonist in wild-type (WT) and *pxr*^{-/-} mice. Mice treated with dextran sulfate sodium (DSS) developed symptoms of IBD typically seen in humans, including body weight loss, diarrhea, rectal bleeding, shortened colon length, and altered intestinal crypt structure³⁴. Treatment of WT mice with the mouse PXR ligand pregnenolone-16 α -carbonitrile (PCN) alleviated IBD symptoms, whereas mice lacking PXR expression were not affected³⁵. Activation of PXR also decreased intestinal permeability in WT and not in *pxr*^{-/-} mice³⁵. The intestinal epithelial assay is considered a direct reflection of epithelial barrier function³⁶ and thus indicates a protective effect on intestinal permeability as a result of PXR activation. These studies also revealed that activation of PXR suppresses expression of the NF- κ B target genes including IL-1 β , IL-10, iNOS, and TNF α , suggesting that PXR dampens the inflammatory response, although other mechanisms for the PXR protection in IBD cannot be ruled out (see below).

Validation of PXR as a potential target for treatment of IBD in humans was demonstrated through study of rifaximin (Xifaxan), a semi-systemic rifamycin-derived antibiotic that exhibits low gastrointestinal absorption while retaining potent antibacterial activity in the gastrointestinal system. The FDA approved Rifaximin in 2004 for the treatment of traveler's diarrhea, and in 2011 for hepatic encephalopathy therapy. The minimal absorption of rifaximin is likely due to its self-association tendency in contrast to oral absorption of other rifamycin derivatives (e.g. rifampicin) that enter the body via passive diffusion. Pharmacokinetic studies in animal models revealed that 80–90% of rifaximin is concentrated in the intestine; less than 0.2% of rifaximin is transported into the liver and kidney, and less than 0.01% is distributed in other tissues³⁷. Clinical pharmacokinetics further showed that serum levels of rifaximin were below the limits of detection in healthy adults following oral administration of rifaximin. In addition, there was no evidence for the accumulation of rifaximin in the body following repeated administration³⁷. These studies confirmed that while rifaximin is not suitable for treating systemic bacterial infections, it could have a distinct advantage on direct therapy of intestinal bacteria to protect intestinal barrier function.

Rifaximin is an intestine-specific human PXR agonist³⁸; treatment of PXR-humanized mice (mice in which the complete human PXR gene was introduced to the *pxr*^{-/-} mice) with rifaximin resulted in significant induction of PXR target genes in the intestine, but had no significant effect on the induction of hepatic PXR target genes³⁸. In contrast, rifampicin, another related antibiotic with oral bioavailability, was able to activate gene expression in both the intestine and liver. Cell-based reporter gene assays demonstrated that rifaximin activates human PXR but not mouse PXR or other nuclear receptors including constitutive androstane receptor (CAR; NR1I3), PPAR α , PPAR γ , and FXR. Rifaximin also reduced NF- κ B signaling in a PXR-dependent manner in primary human colon epithelial cells as well as in human colon biopsies³⁹. The preventive and therapeutic role of rifaximin in experimental models of IBD was demonstrated in the PXR-humanized mouse where rifaximin not only prevented IBD before an inflammatory insult, as revealed by use of the DSS and 2,4,6-trinitrobenzene sulfonic acid (TNBS) mouse models of IBD, but also decreased the symptoms after the onset of colitis⁴⁰. Conversely, rifampicin had no impact on experimentally-induced IBD. Among the possible reasons that rifampicin cannot protect against IBD is that rifampicin markedly reduces the hepatic expression of stearoyl-CoA desaturase-1 (SCD-1) due to its high systemic bioavailability, in contrast to the minimal absorption of rifaximin in the circulation⁴⁰. Reduced SCD-1 results in lower levels of unsaturated lysophosphatidylcholine in plasma, which is among the most important anti-

inflammatory unsaturated fatty acids⁴¹. Clinically, rifaximin appears to have more efficacy in the therapy of CD than do traditional medications used to treat IBD such as metronidazole and/or ciprofloxacin^{42–43}, due in part to its well-tolerated and efficient effects in adult CD patients⁴⁴ as well as for pediatric IBD⁴⁵. Several clinical trials demonstrated that rifaximin decreased intestinal permeability in adult/pediatric patients with gastrointestinal diseases, such as small intestine bacterial overgrowth⁴⁶ or tropical enteropathy⁴⁷. These data provide evidence for the use of rifaximin in intestinal disorders and firmly establish a role for PXR in IBD therapy⁴⁰ (Figure 1).

Other evidence for the involvement of PXR in protection against IBD was obtained with curcumin. Curcumin is a spice and dietary supplement that demonstrates preventive effects on IBD in a mouse model⁴⁸. Among the possible mechanisms proposed for effect of curcumin on IBD is that curcumin activates human PXR, as revealed by increased *CYP3A4* promoter luciferase activity in HepG2 cells⁴⁹. Curcumin significantly reduces the histological signs of colonic inflammation in *mdr1a*^{-/-} mice⁵⁰; *mdr1a* is a gastrointestinal transporter that is induced by PXR⁵⁰, and thus the protection by curcumin on *mdr1a*^{-/-} mice is assumed through PXR activation. Solomonsterol A, a newly-reported PXR agonist extracted from the sponge *Theonella Swinhoei*, also protects against the development of clinical signs and symptoms of colitis through reduction of TNF α in PXR-humanized mice⁵¹. These studies suggest that PXR agonists hold promise in the treatment of inflammation-driven immune dysfunction in clinical settings.

PXR role in IBD pharmacotherapy

IBD treatment regimens depend on the level of severity of the disease. Drug treatments include combined administration or administration alone of aminosalicylates, immunosuppressive drugs, antibiotics, and corticosteroids⁵². Many of the drugs used in the conventional therapy of IBD are metabolized and transported by CYP3A4 and P-glycoprotein (P-gp), respectively⁵². Thus, PXR agonists (e.g. rifaximin, rifampicin³¹, St John's wort²⁷ etc.) and PXR antagonists (e.g. ketoconazole, itraconazole, fluvoxamine or grapefruit juice²⁷) would affect the pharmacokinetics of CYP3A4 drug substrates due to its activation or lack of activation²⁷. For example, corticosteroids are the most widely used drugs in IBD treatment due to their immunosuppressive activity and long biological half-life. However, the area under the curve (AUC) of budesonide, an efficient corticosteroid used in IBD treatment, increased by 6.5-fold when co-administrated with ketoconazole, compared to a 3.8-fold increase in the AUC when these two drugs were administered 12 hours apart⁵³. Thus, dosage reductions of the corticosteroids are applied when inhibitors of CYP3A4 metabolism or induction are used concomitantly with corticosteroids.

Altered expression of drug transporters can also impact IBD therapy. For example, mesalazine, an aminosalicylate drug used to treat IBD, is metabolized into *N*-acetyl-mesalazine that is transported by P-gp. High expression of P-gp was associated with failed treatment of mesalazine in IBD patients⁵⁴. In addition, cyclosporine, a common immunosuppressive drug sometimes used in IBD, is extensively metabolized by CYP3A4 and transported by P-gp. PXR agonists can increase hepatic clearance of cyclosporine and reduce its bioavailability⁵⁵.

Clinical reports revealed that rifaximin alone or in combination with other antibiotics appeared to have a significant effect at inducing remission in active IBD⁵⁶. Because rifaximin is a gut-specific agonist of human PXR³⁸, one plausible mechanism is that rifaximin induces CYP3A4 leading to clinically significant reductions in the bioavailability of established drugs that are CYP3A4 substrates. Coupled with increased clearance, this induction of CYP3A4 may reduce the possibility of drug-induced hepatic or renal toxicity. Therefore, it remains to be determined whether modulation of the pharmacokinetic

properties by PXR increases the desired effects and simultaneously reduces the typical systemic adverse effects of IBD drugs, especially when used in combination with other agents.

Mechanisms for the influence of PXR on IBD

Polymorphisms of PXR in IBD

Evidence from several studies suggests that xenobiotic metabolism may play a role in IBD and that low levels of PXR may be associated with disease expression. An Irish cohort including 422 patients with IBD and 350 ethnically matched controls was examined for single nucleotide polymorphisms (SNPs), and several polymorphisms were identified in the *PXR* gene that were over-represented in IBD patients as compared with controls⁵⁷. Moreover, an independent study identified other SNPs in the *PXR* gene that were associated with CD but not with UC in Caucasian patients⁵⁸. Evaluation of a Spanish cohort of 365 UC and 331 CD patients, and 550 ethnically matched controls showed significant differences in the overall haplotype of IBD between UC and CD patients⁵⁹ in *PXR* SNPs. Although these studies have shown a genetic association of *PXR* with IBD, it is important to note that others did not find an association between the *PXR* polymorphism and IBD through the analysis of 187 pediatric IBD patients and 185 controls⁶⁰. Although the results are mixed, an association of genetic variation in the *PXR* gene with susceptibility to IBD cannot be ruled out. However, it needs to be emphasized that functional analysis of the roles of any SNPs in and around the *PXR* gene on PXR expression and activity have not been done to establish a mechanistic basis for the association with IBD.

PXR modulation of NF- κ B

Reciprocal crosstalk between PXR and NF- κ B may be the mechanism for the anti-inflammatory properties of PXR²⁸. The NF- κ B family comprises five members, namely p65 or Rel A, Rel B, Rel C, p50, and p52, and is a key regulator of inflammation and the innate and adaptive immune responses⁶¹. NF- κ B normally remains in the cytoplasm bound to the protein inhibitor of NF- κ B (I κ B). Activating signals, such as proinflammatory cytokines, reactive oxygen species, and viral products lead to phosphorylation and degradation of I κ B, thus allowing NF- κ B to translocate to the nucleus and directly regulate the expression of its target genes⁶². NF- κ B signaling is significantly inhibited following PXR activation⁶³. Consistent with this data, *pxr*^{-/-} mice showed an increase in NF- κ B target gene expression and demonstrated chronic inflammation in the small intestine²⁸. In addition, PXR silencing increased expression of TNF- α , IL-8, and other proinflammatory cytokines, and decreased transforming growth factor β (TGF- β) and interferon-gamma-inducible 10 kD protein (IP-10) in primary fetal human colon epithelial cells³⁹ as well as human hepato⁶⁴-or colon carcinoma cell lines³⁹⁻⁴⁰. Exposure to rifaximin caused a robust attenuation of inflammatory mediators and increased the generation of TGF- β ³⁹. PXR silencing by siRNA completely abrogated these anti-inflammatory effects of rifaximin, due to less binding of NF- κ B with PXR. Additional clues emerged when it was reported that NF- κ B can directly interact with RXR α ⁶³, an essential dimerization partner for various nuclear receptors such as PXR. PXR binds to response element of target genes as a heterodimer with RXR α ⁶³. Because NF- κ B interferes with RXR α binding, activated NF- κ B could reduce PXR transactivation activity via interference with RXR α . This mechanism of suppression by NF- κ B may be extended to other nuclear receptor-regulated systems in which RXR α is a dimerization partner (Figure 2).

Likewise, the crosstalk between pattern recognition receptors (PRR) and PXR might also be through NF- κ B binding to RXR α . The innate immune system, initiated by PRR provides the first line of host defense against invading pathogens⁶⁵. Toll-like receptors (TLRs), a family

of PRR that sense a wide range of microorganisms, are expressed in the intestine and are critical for intestinal homeostasis^{66–67}. Cytoplasmic PRR, such as NOD2-like receptor (NLR), detect pathogens that have invaded the cytosol and are involved in the pathogenesis of CD⁶⁸. Lipopolysaccharide (LPS)-mediated induction of pro-inflammatory cytokines activate a variety of cell-signaling kinases including c-Jun N-terminal kinase (JNK) and NF- κ B⁶⁹. Activation of JNK by LPS results in modification of RXR α , leading to suppression of PXR/RXR α hepatic target genes⁶⁹. Lipoteichoic acid, a toxic bile acid, can induce TLR2 and the pro-inflammatory cytokines, JNK and NF- κ B. Subsequently, PXR and CAR and its target genes are rapidly and significantly repressed⁷⁰ (Figure 3). In all, the relationship between NF- κ B and PXR is likely a mechanism that mediates the protective effects of PXR in inflammatory diseases, thus establishing a signaling network involving PXR with NF- κ B as a central hub.

Post-translational modulation of PXR

In addition to the possible modulation of NF- κ B through RXR α -PXR, post-translational modulation of PXR by ubiquitylation⁷¹, phosphorylation⁷², SUMOylation⁷³, and acetylation⁷⁴ could impact inflammation (Figure 3). Serological biomarkers in IBD indicate that ubiquitination factor E4A (UBE4A), a U-box-type ubiquitin-protein ligase, is upregulated in IBD. Higher levels of anti-UBE4A IgG were associated with severe syndromes⁷¹. Although UBE4A expression is low in the cytoplasm of enterocytes and goblet cells, immunohistological analysis showed that UBE4A expression was highly elevated only in entero-endocrine cells of ileal mucosa from CD patients, and not in normal subjects⁷⁵. Additionally, PXR and CYP3A4 ubiquitination increases during inflammation in the small intestine⁷⁶. Thus, repression of PXR through up-regulated ubiquitylation in IBD might raise the activity of NF- κ B and thus induce the inflammatory response.

In IBD, cyclic AMP-dependent protein kinase (PKA) signaling is activated⁷⁷. PXR can serve as a substrate for catalytically-active PKA *in vitro*, as revealed by the up-regulation of PXR in mouse hepatocytes by the PKA activator 8-bromo-cyclic AMP⁷². PXR activity can potentially be regulated by phosphorylation at specific amino acid residues within several predicted consensus kinase recognition sequences to differentially affect PXR biological activity. The amino acid residues Thr57, Ser208, Ser305, Ser350, and Thr408 are thought to be critical phosphorylation sites regulating the biological activity of the PXR⁶⁸. Mutations at positions Thr57 and Thr408 abolish ligand-inducible PXR activity, whereas mutations at Ser8, Ser305, Ser350, and Thr408 of the extreme N-terminus and in the PXR ligand-binding domain, decrease the ability of PXR to form heterodimers with RXR⁷⁸. The subcellular localization of the PXR protein is also profoundly affected by mutations at Thr408. Thr57 abolishes transactivation activity and alters nuclear localization pattern of human PXR⁷⁹. These studies confirm that the activity of PXR is modulated by changes in its overall phosphorylation status⁸⁰. Determining whether phosphorylation of PXR at specific sites regulates inflammation in IBD remains an open and important question for future studies.

A recent report revealed that SUMOylated PXR directly represses NF- κ B in liver⁷³. SUMOylation is a post-translational modification involved in various cellular processes, such as nuclear-cytoplasmic transport, transcriptional regulation, apoptosis, protein stability, response to stress, and progression through the cell cycle. This analysis revealed that the human PXR protein can serve as an effective substrate for human SUMO1, SUMO2, or SUMO3 in the SUMO-conjugation pathway and that the SUMOylation sites serve as a functional link between ligand-activated PXR and its ability to transrepress NF- κ B activity⁷³. In addition, the effect of PXR acetylation and metabolic status on ligand-mediated PXR gene activation pathways is observed in patients with morbid obesity, hepatic steatosis, and non-alcoholic steatohepatitis, although the potential role is not determined⁷⁴.

Inhibition of T lymphocyte proliferation by PXR

The intestine is the largest lymphoid organ in the body because of the huge antigen load to which it is exposed on a daily basis⁸¹. Many studies have shown that activated T cells mediate chronic intestinal inflammation⁸². PXR is expressed in human CD4, CD8, CD19, and CD14 cells⁸³. 8-Methoxypsoralen (8-MOP), a prototype photochemotherapeutic agent used to repress cutaneous T-cell lymphoma, activates PXR⁸⁴. Cyclosporine A, a PXR agonist which is intravenously administered to treat steroid-refractory severe UC, inhibits T-cell function⁸⁵. Upon immune stimulation, activation of PXR inhibits T lymphocyte proliferation and anergizes T lymphocytes by decreasing the expression of CD25 and IFN- γ and decreasing phosphorylated NF- κ B and MEK1/2 in mouse and human T lymphocytes⁸⁶. Conversely, *pxr*^{-/-} mice exhibit an exaggerated T lymphocyte proliferation and increased CD25 expression⁸⁶. Furthermore, PXR-deficient lymphocytes produce more IFN γ and less anti-inflammatory cytokine IL-10⁸⁶. Thus, the immune-regulatory role of PXR in T lymphocytes may contribute to the suppression of T lymphocyte proliferation in IBD (Figure 3).

Concluding remarks

In summary, PXR exerts a positive therapeutic role in IBD through mechanisms involving feedback with NF- κ B, TLR, NOD2, and modulation of T lymphocytes. The coordinate regulation between PXR and other nuclear receptors may also be important due to similar mechanisms involving modulation of the NF- κ B signaling cascade. Rifaximin and other novel candidate drugs as possible novel agents for the treatment of IBS and IBD based on PXR-targeted therapy need further attention. Although rifaximin has shown promise for IBD therapy in clinical trials, concerns have been raised about the development of antibiotic resistance because patients will be administered the drug for long periods of time⁸⁷. Thus, if the effect of rifaximin on IBD is due to its activation of PXR and not through its bacterial killing properties, other gut-specific PXR ligands that do not have antibiotic activities could be developed. As patients with IBD are six times more likely to develop colorectal cancer, PXR and related drug treatment for IBD might be a target for chemoprevention of colon carcinogenesis. Although a few reports on the role of PXR in colon cancer have been published, the results are still controversial⁸⁸⁻⁸⁹. More studies on the role of PXR in colitis-associated colon cancer are warranted. The importance of PXR in IBD is becoming increasingly clear. A complete understanding of the role and regulation of PXR in IBD is progressing quickly and may be useful for the development of novel strategies to better predict, prevent and treat of IBD.

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Fig 1. Rifaximin repression of IBD via human PXR regulation

Chemically-induced IBD destroys the structure and function of normal epithelial cells and expression of DMEs (A), due in part to activation of NF- κ B and increased proinflammatory cytokines. (B) following an imbalance of the epithelial barrier and mucosal immune system and increase of intestinal permeability. However, upon rifaximin-induced PXR activation in epithelial cells, the NF- κ B signaling cascade is repressed and cytokine production is inhibited, associated with suppression of intestinal permeability through PXR activation. This restores the balance between the epithelial barrier and mucosal immune system, resulting in the reconstruction of cell structure and function (C). DMEs: drug metabolism enzymes.

Fig 2. The cross-inhibition between PXR and NF-κB

NF-κB contains two major components, p65 and p50. PXR/RXR heterodimer auto-bind with CBP, PCAF and HAT initially to regulate transcription. NF-κB can directly interact with the RXR. Thus, one possibility to explain the link between NF-κB and PXR is through the binding of p65 and RXR. This binding is triggered upon ligand binding of PXR response element. The binding between p65 and RXR may also interfere with the formation of the p65-p50 complex and subsequent DNA binding. CBP: CREB-binding protein, PCAF: P300/CBP-associated factor, HAT: histone acetyltransferase, H3/H4: histones. Cytokines are IL-8: interleukin 8, IκBα: IκBα-NFκB complex, IFNβ: interferon-beta, MCP-1: monocyte chemotactic protein-1, TNFα: tumor necrosis factors alpha.

Fig 3. Multiple signaling cascades to repress IBD via PXR modulation

Crosstalk between PXR and NF- κ B, through direct action of PXR by ubiquitylation, phosphorylation, SUMOylation, and acetylation could impact inflammation (I), as well as germline-encoded pattern recognition receptors (PRR, including TLR/NOD2) activation of JNK or IKK by LPS resulting in the modification of RXR α , leading to suppression of PXR/RXR α -dependent hepatic genes (DMEs, drug metabolism enzymes) (II). In addition, PXR inhibits T lymphocyte proliferation by decreasing expression of cytokines of CD25 and IFN γ and decreasing phosphorylation of NF- κ B in mouse and human T lymphocytes (III). JNK: c-Jun NH(2)-terminal kinase, IKK: I κ B kinase, CD25:alpha chain of the IL-2 receptor, IFN γ : Interferon-gamma.