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Special Section on Xenobiotic Receptors—Minireview

Microbial Metabolites as Ligands to Xenobiotic Receptors: Chemical Mimicry as Potential Drugs of the Future

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ABSTRACT

Xenobiotic receptors, such as the pregnane X receptor, regulate multiple host physiologic pathways including xenobiotic metabolism, certain aspects of cellular metabolism, and innate immunity. These ligand-dependent nuclear factors regulate gene expression via genomic recognition of specific promoters and transcriptional activation of the gene. Natural or endogenous ligands are not commonly associated with this class of receptors; however, since these receptors are expressed in a cell-type specific manner in the liver and intestines, there has been significant recent effort to characterize microbially derived metabolites as ligands for these receptors. In general, these metabolites are thought to be weak micromolar affinity ligands. This journal anniversary minireview focuses on recent efforts to derive potentially nontoxic microbial metabolite chemical mimics that could one day be developed as drugs combating xenobiotic receptor–modifying pathophysiology. The review will include our perspective on the field and recommend certain directions for future research.

SIGNIFICANCE STATEMENT

Xenobiotic receptors (XRs) regulate host drug metabolism, cellular metabolism, and immunity. Their presence in host intestines allows them to function not only as xenosensors but also as a response to the complex metabolic environment present in the intestines. Specifically, this review focuses on describing microbial metabolite–XR interactions and the translation of these findings toward discovery of novel chemical mimics as potential drugs of the future for diseases such as inflammatory bowel disease.

Introduction

Xenobiotic receptors or, more appropriately, xenobiotic nuclear receptors [NRs; specifically, the arylhydrocarbon receptor (AHR), the farnesoid X receptor (FXR), the liver X receptor (LXR), the constitutive androstane receptor (CAR), the pregnane X receptor (PXR), the retinoid X receptor (RXR), and their functionally related receptors] are promiscuous ligand-binding proteins that function as sensors for the presence of foreign chemicals, either in their native or metabolized state, and regulate their metabolic clearance from the body (Xie and Evans, 2001; Wallace and Redinbo, 2013). These receptors function as ligand-regulated transcription factors resulting in the induction of gene promoter-specific transcription. Recent studies have demonstrated that these xenobiotic receptors can bind to microbially derived metabolites and that these receptors function beyond metabolism in regulating inflammation, immunity, and other aspects of host physiology (Nieves et al., 2022). The goal of this minireview is to update new findings of microbial metabolite–NR interactions with an emphasis on intestinal physiology, (Guan et al., 2021) and, with this knowledge, demonstrate recent advances in developing potent microbial metabolite mimics as potential drugs of the future (Nuzzo and Brown, 2020). It is essential to point out that the authors have previously published reviews on this topic (Dvořák, Klapholz et al., 2020; Dvořák, Sokol et al., 2020, Dvořák et al., 2021); however, here, we will only provide new updates to this field of research (Li et al., 2020).

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ABBREVIATIONS: AHR, arylhydrocarbon receptor; CAR, constitutive androstane receptor; CYP, cytochrome; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IPA, indole 3-propionic acid; LXR, liver X receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NR, nuclear receptor; PPAR, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; RXR, retinoid X receptor; TLR, toll-like receptor; XR, xenobiotic receptor.

Brief Historical Perspective

Gastrointestinal immune balance significantly depends on the function of NRs (Schmidt and Mangelsdorf, 2008; Klepsch et al., 2019). The major xenobiotic receptors are expressed abundantly in the intestinal epithelium and the microenvironment (including the immune cell compartment), AHR (epithelium and mucosal immune cells), FXR (epithelium), CAR (epithelium and immune cells), LXR (epithelium and immune cells), PXR (epithelium > immune cells), and RXR (epithelium and immune cells). Related receptors such as peroxisome proliferator-activated receptor (PPAR) will only be mentioned where relevant concerning microbial metabolite ligands (Modica et al., 2010).

Arylhydrocarbon Receptor. The mammalian AHR is a transcription factor belonging to the basic helix-loop-helix (bHLH)-PAS family of transcription factors. AHR activation is ligand-dependent. Upon binding with specific ligands, AHR translocates from the cytoplasm to the nucleus, being chaperoned by proteins such as heat shock protein 90, hepatitis B virus X-associated protein, and p23. In the nucleus, it dimerizes with AHR nuclear translocator. The latter is required for DNA binding and AHR transcriptional activity (Stockinger et al., 2021). Historically, AHR is an evolutionarily conserved environmental sensor and a critical pathway facilitating the toxic effects of environmental toxins. However, more recently, this viewpoint has expanded to include a two-faced receptor with perhaps beneficial functions seen in the context of immune cells and "nontoxic" natural ligands. Under homeostatic conditions, AHR involvement might be subtle, but its role becomes important during pathology (e.g., regeneration following tissue injury) (Stockinger et al., 2021). Microbial indoles are known ligands of AHR (Zelante et al., 2013; Pernomian et al., 2020; Scott et al., 2020; Dvořák et al., 2021; Gasaly et al., 2021; Wang et al., 2022).

Farnesoid X Receptor. The FXR was first identified by Forman et al. (1995). Bile acids (e.g., chenodeoxycholic acid) serve as their physiologic ligands (Gustafsson 1999; Kliewer et al., 1999). FXR is also a ligand-driven transcription factor that heterodimerizes with RXRα and drives gene/promoter-specific transcription. Bile acids, via FXR, induce fibroblast growth factor (FGF) 15/FGF19. The latter is a hormone secreted by the intestinal epithelial cells into the enterohepatic circulation. FGF15/FGF19 activates hepatic FGF receptor 4-β-klotho receptor complexes. In this manner, FXR signaling regulates gene expression involved in cholesterol, bile acid, and lipid metabolism, as well as that regulating cell proliferation. Agonists for FXR and analogs for FGF15/19 are currently being developed as drugs combating metabolic syndrome and cholestatic diseases (Katafuchi and Makishima, 2022; Panzitt et al., 2022). Bacterial metabolites, although not chemically characterized, serve as FXR ligands (Zhang et al., 2015). More recently, microbial bile acids have been shown to function as FXR ligands (Schoeler and Caesar, 2019; Guzior and Quinn, 2021; Xiang et al., 2021; Yan et al., 2021; Cai et al., 2022), and this pathway is relevant to humans with inflammatory bowel disease (Wilson et al., 2020). Microbial bile acids also regulate the levels of colonic retinoic acid receptor-related orphan receptor γ^+ regulatory T (T_{reg}) cells, which reduces intestinal inflammation in appropriate colitis models (Song et al., 2020). Other microbial metabolites serving as ligands for FXR include altenusin, a nonsteroidal fungal metabolite (Zheng et al., 2017).

Liver X Receptor. The LXR, assigned initially as an orphan receptor, was later deorphanized with the discovery of oxygenated cholesterol derivatives such as oxysterols (Janowski et al., 1996). This receptor is a master regulator of cholesterol metabolism (Peet et al., 1998). More recently, the receptor has had significant pharmacologic effects on various diseases, including obesity, diabetes, and autoimmunity, to name a few (Viennois et al., 2011). LXR regulates intestinal immunity, modulating receptor-related orphan receptor γt^+ T_{reg} and Th17 cells in the mesenteric lymph nodes through distinct mechanisms (Jakobsson et al., 2014; Parigi et al., 2021). Steroidal and triterpenoidal fungal metabolites are LXR ligands (Ondeyka et al., 2005). Hydroxy and oxo fatty acids, produced by microbes (e.g., lactobacillus) metabolizing unsaturated fatty acids, serve as efficient LXR ligands (Nanthirudjanar et al., 2015). Microbial metabolites of citrus pectin oligosaccharides are also LXR ligands and have been shown to exhibit anti-inflammatory properties (Hu et al., 2021).

Constitutive Androstane Receptor. The CAR is a constitutive transactivator and undergoes ligand-mediated translocation to the nucleus to exert full genomic effects. In addition, CAR has ligand-independent effects (e.g., via kinase signaling) that can also result in gene transcription (Mackowiak and Wang, 2016). It is expressed in the liver and small intestines (Qatanani and Moore, 2005). CAR is also a regulator of drug metabolism but has a more comprehensive role in modulating intestinal inflammation (Qatanani and Moore, 2005). Multiple microbial indoles can activate CAR (Venkatesh et al., 2014), but the significance of these interactions remains unknown.

Pregnane X Receptor. The PXR, a master regulator of xenobiotic metabolism (Kliewer, 2015), is now an established (agonist) target for the prevention of colitis and colitis-induced colon cancer (Cheng et al., 2012). This receptor forms a complex with its obligate heterodimeric partner, the RXR (NR2B1). The receptor complex binds response elements in the promoters and enhancers, usually in the form of direct (DR3, DR4) or averted (ER6) repeats of the consensus motif AG(G/T)TC(A/C) (Goodwin et al., 1999). Transcriptional induction follows the recruitment of the p160 family and other coactivators but with a complex interplay with other regulators, such as co-repressors. In terms of its canonical role in drug metabolism, PXR was discovered in 1998 (Bertilsson et al., 1998; Blumberg and Evans, 1998; Kliewer et al., 1998) and described as a master regulator of drug metabolism in that PXR can enhance the clearance of its own xenobiotic ligands via enzymatic (phases I and II) and transporter-mediated (phase III transporters) effects. In addition, PXR is an important mediator of drug–drug interactions when multiple drugs are coadministered (Goodwin et al., 1999; Wang et al., 2014; Shehu et al., 2016; Nicolussi et al., 2020, Wang et al., 2020; Hall et al., 2021). PXR also has a role in bile acid metabolism, acting on feedback and feed-forward mechanisms to alter bile acid production from cholesterol (Handschin and Meyer, 2005). PXR has a very promiscuous ligand binding pocket, allowing for various xenobiotic interactions (Orans et al., 2005). Specific interactions of interest include the effect of the antitubercular drug rifampicin on isoniazid-mediated hepatotoxicity via the accumulation of the endogenous hepatotoxin protoporphyrin IX in the liver (Li, Lu et al., 2013). PXR may prognosticate for survival in patients undergoing liver transplantation (Amer et al., 2019), perhaps via its effects on tacrolimus metabolism (Stifft et al., 2018). In addition, recent work has highlighted new roles for PXR as a factor promoting radio resistance in cancer (Niu et al., 2022) and drug sensitivity or resistance (Creusot et al., 2020; Sári et al., 2020; Matheux et al., 2021; Ozawa et al., 2021) and promotes striated and smooth muscle metabolism and physiology (Swales et al., 2012; Zhang et al., 2019; Ortiz-Flores et al., 2020). Our prior work demonstrated that gut microbe-produced indole metabolites of L-tryptophan (e.g., indole and indole propionic acid) are ligands of PXR (Venkatesh et al., 2014). To develop nontoxic yet "nature"-inspired agonists for PXR, we developed synthetic analogs mimicking the binding of indole pharmacophore on PXR. These PXR-selective leads, FKK5 and FKK6, are potent inhibitors of intestinal inflammation in organoids and mice (Dvořák, Kopp et al., 2020). We termed this concept *microbial metabolite mimicry*, which has been reviewed as a new approach to the drug discovery (Nuzzo and Brown, 2020). These compounds are,

however, synthetic intermediates in the chemistry toward a dual indole structure (a requirement called for by the simultaneous binding of multiple indoles on PXR). It is important to note, however, that, to date, no crystal structure studies have been published with microbial metabolites or their mimics and PXR. This contrasts with the availability of structures demonstrating synergistic binding of select endocrine-disrupting molecules within the PXR ligand-binding domain (Delfosse et al., 2021). Other microbially derived metabolites of bile acid (lithocholic acid) and vitamin metabolism (vitamin K2) are PXR ligands and drive metabolic maturation of pluripotent stem cells and fetal hepatocytes (Avior et al., 2015).

The FKK5 and FKK6 compounds at the schedule and concentrations reported do not seem toxic to mice; however, these results are unpublished and would need confirmation in larger animals and other rodent models. To this end, it is known that systemic PXR activation can result in deleterious consequences such as hyperlipidemia and adverse changes in blood pressure and glucose metabolism (Rysä et al., 2013; Hassani-Nezhad-Gashti et al., 2020; Rahunen et al., 2022). In this context, PXR is expressed at the protein and mRNA level in microdissected human intestines (epithelial mucosa) and the liver (Miki et al., 2005; Godoy et al., 2013). Interestingly, even in total liver mRNA analysis, PXR was the most abundant compared with related receptors, AHR, and CAR (Liu, Lu et al., 2021). Others have reported cell-specific XR signatures in the intestines (Modica et al., 2010). On a functional level, it is clear that PXR is present in the liver as potent ligands such as hyperforin have resulted in drug interactions in humans (Nicolussi et al., 2020). PXR can also modulate the drug hepatotoxicity (Shehu et al., 2021). Thus, our goals are to formulate FKK5 and FKK6 for locoregional (colonic) delivery with limited systemic bioavailability.

Since the publication of our original paper on microbial metabolites and PXR (Venkatesh et al., 2014), several groups have independently replicated our findings concerning indole 3-propionic acid (IPA) and its effects on mouse intestinal barrier function (Dodd et al., 2017) and have found that IPA abrogates intestinal inflammation (Konopelski and Mogilnicka, 2022), IPA action partly depends on PXR (Pulakazhi Venu et al., 2019; Xiao et al., 2020; Du et al., 2021), PXR inversely regulates toll-like receptor (TLR) 4 (Esposito et al., 2016; Huang et al., 2018; Erickson et al., 2020; Lu et al., 2021; Su et al., 2022; Yuan et al., 2022), epithelial TLR4 regulates inflammation and tumors (Fukata et al., 2011; Sodhi et al., 2012; Burgueño et al., 2021), as well as the discovery of additional indole microbial metabolites (e.g., indole acetamide) with weak effects on PXR (Illés et al., 2020). Two reports from the same investigators challenge the notion that epithelial TLR4 is functional (Crame et al., 2021; Tam et al., 2022); however, further work is needed to clarify this discrepancy as these observations are likely to be context- and model-specific (Gribar et al., 2008; Takahashi et al., 2009; Soliman et al., 2010; Nanthakumar et al., 2011; Sodhi et al., 2012, Li et al., 2014; Belmonte et al., 2016; Dheer et al., 2016; Kim et al., 2016; Coleman and Haller, 2017; Inoue et al., 2017; Hu et al., 2018; Latorre et al., 2018; Price et al., 2018; Nighot et al., 2019; Stephens and von der Weid, 2020; Burgueño et al., 2021; Chen, Zhang et al., 2021; Kayisoglu et al., 2021; Qi-Xiang et al., 2022; Sodhi et al., 2022; Zhou et al., 2022). IPA is a weak human PXR (steroid and xenobiotic receptor ligand) (Venkatesh et al., 2014); in keeping with this, intercellular permeability is not altered in the human caco-2 cells (Scott et al., 2020). Another downstream effector of intestinal inflammation is dysregulated NF-κB signaling in both immune and epithelial cells. In this context, epithelial NF-κB signaling is thought to be essential for the maintenance of epithelial self-renewal and the maintenance of a proper balance between Paneth and goblet cells (Brischetto et al., 2021). In our context, however, PXR inhibits NF-κB signaling (Shah et al., 2007; Bautista-Olivier and Elizondo, 2022), creating an apparent contradiction. However, it is known that noncanonical epithelial NF-κB via the supplementation of RelA dimers to the canonical NF-κB modules exacerbates intestinal inflammation (McDaniel et al., 2016; Ke et al., 2019; Ramakrishnan et al., 2019; Chawla et al., 2021). Hence, it is conjectured that PXR may inhibit the noncanonical NF-κB or normalize epithelial NF-κB signaling pathways within the in vivo context of intestinal inflammation (Guma et al., 2011; Kaci et al., 2011). Indeed, since PXR activation also prevents colitis-induced cancer, PXR may be involved in inhibiting the IKK2/NF-κB signaling pathway in epithelial cells (Vlantis et al., 2011).

Microbial indole metabolite biomimicry has been successful for receptors beyond PXR (Dvořák, Klapholz et al., 2020, Dvořák, Sokol et al., 2020, Li et al., 2020). IPA has several complementary host targets, which further asserts the premise that IPA inhibits inflammation (Alexeev et al., 2021; Sári et al., 2020). In this context, indole acts to mitigate cytotoxicity by *Klebsiella spp*. via suppression of toxin production, enhanced conversion of tilimycin (cytotoxin) to tilivalline (less potent cytotoxin) and activation of PXR (Ledala et al., 2022). Indeed, IPA may promote nerve regeneration by an unknown mechanism partly dependent on PXR (Serger et al., 2022). Additionally, PXR activation is expressed in platelets. It inhibits platelet-mediated thrombosis in mice expressing the human PXR transgene, perhaps via nongenomic inhibition of the Src family of kinases (Flora et al., 2019).

Retinoid X Receptor. The RXR integrates signaling via several NRs by heterodimerization. RXR dimers signal via binding to specific DNA sequences on gene promoters. RXR interacts with ligands that are specific to the receptor (e.g., 9-*cis*-13,14-dihydroretinoic acid), and these ligands are endogenous or exogenous xenobiotics (e.g., organotins). However, to date, microbial metabolite ligands that specifically bind RXR have not been described, although it is conceivable that low-affinity promiscuous ligands are present in the microbial metabolome with RXR binding properties (Brtko and Dvořák, 2020). However, a dietary microbial metabolite of chlorophyl A, phytol, and itsmetabolites, phytanic and pristanic acids, are ligands of RXR and one heterodimeric partner, P PARα and P PARγ (Bobe et al., 2020). Other known microbially derived ligands to PPARγ include conjugated linoleic acid (Bassaganya-Riera et al., 2012) and indole metabolites (Venkatesh et al., 2014; Tsukidate et al., 2020). More recently, inosine, a gut microbial metabolite, has been described as a PPARγ signaling activator that attenuates colitis in mice (Li et al., 2021).

Endogenous Microbially Derived Ligands for XRs and Their Use as Potential Therapeutic Agents. Various microbially derived metabolites serve as ligands to xenobiotic NRs. Microbial metabolites with host protective properties (e.g., intestinal inflammation/obesity and short-chain fatty acids, indole metabolites), per se, have been proposed as sources for developing new drugs (Giddings and Newman, 2013; Saha et al., 2016; Stringlis et al., 2018; Descamps et al., 2019; Raihan et al., 2021; Ramírez-Rendon et al., 2022). The use of purified microbial metabolites as drugs has had mixed results. Considerable caution is advocated in this approach, especially with high or chronically administered doses of the microbial metabolite in question (Lee, Ecton et al., 2020; Konopelski et al., 2021; Liu, Sun et al., 2021; Sehgal et al., 2021; Chen et al., 2022; Paeslack et al., 2022; Teng et al., 2022; Zhang, Jiang et al., 2022). For example, several microbial metabolites have been proposed to partly function as antioxidants, such as microbial "green tea" metabolites (Pérez-Burillo et al., 2021). However, not all molecules with antioxidant function remain beneficial when used in large doses. Vitamin C (ascorbic acid) has been proposed as a potent anti-infective and antisepsis agent (Kuhn et al., 2018; Moskowitz et al., 2018; May et al., 2021). Yet, recent randomized clinical studies have questioned such benefits (Assouline et al., 2021; Sevransky et al., 2021) and demonstrated an even higher risk of death from intravenous ascorbic acid

(Lamontagne et al., 2022). It is likely that indiscriminate applications of antioxidants may result in a similar fate and should be approached with caution (Ye et al., 2022). With that said, one must be cautious the other way in interpreting all indole metabolites, even uremic toxins, as uniformly injurious to health (Vanholder et al., 2022).

Key Recent Advances

One alternative approach to the therapeutic use of endogenous microbial metabolites requires that microbial ligands bind xenobiotic receptors (XR). The metabolite should be amenable to easy chemical analog synthesis. The metabolite should serve as potent XR ligands and affect host physiology in the desired manner. These microbial metabolite mimics could be developed into new drugs. The requisite here is that the mimics must be nontoxic to the host. Thus, not all ligand–receptor pairs would be amenable to such an approach. We have termed this approach *microbial metabolite mimicry* (Dvořák, Sokol et al., 2020).

Arylhydrocarbon Receptor. Microbially derived ligands of AHR include short chain fatty acids (e.g., butyrate) are products of the gut microbiome (Marinelli et al., 2019). By contrast, however, butyrate was found only to induce AHR expression but not to serve as a direct ligand (Jin et al., 2017; Jourova et al., 2022; Modoux et al., 2022). The overall result in an intact host may be additive or synergistic; AHRs, while induced by short chain fatty acids, are activated by resident ligands that are also derived from the microbiota (Modoux et al., 2022). For example, indoles derived from the tryptophan metabolism are efficient AHR ligands (Rothhammer et al., 2016). The indole scaffold is a promising chemical moiety for drug mimicry (Dvořák, Klapholz et al., 2020). This scaffold is built on the observation that the microbial metabolite, indole, and its metabolites are endogenous AHR ligands (Hubbard et al., 2015; Lamas et al., 2016). Indeed, potent drug leads, PY109 and PY108, were developed for AHR using indole as the primary chemical scaffold (Chen et al., 2020). Other AHR mimics include the triarylmethanes (Goya-Jorge et al., 2020). More recently, it was shown that a chemically stable form of *Thermosporothrix hazakensis* metabolite 2-(1'*H*-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester, 2-(1*H*-indole-3-carbonyl)-*N*-methyl thiazole-4-carboxamide is a nanomolar potency AHR activator (Grycová et al., 2022). Recently, a 2.85 Å cryo-EM crystal structure was submitted for binding the heat shock protein 90–hepatitis B virus X-associated protein–AHR complex, which provides the first structural visualization of the PAS B domain attached to indirubin (J. Gruszczyk et al., preprint, DOI: https://doi.org/10.1101/2022.05.17.491947). These developments should promote the discovery and characterization of microbial metabolites that serve as AHR ligands. Another recent advance, at least conceptually, calls for studying microbial metabolites combined at their physiologically relevant concentrations. Groestlinger et al. (2022) show that combining urolithin A, alternariol, and deoxynivalenol yields different effects on gut barrier function when each is used alone. Indeed, newer tryptophan microbial metabolites are being evaluated as AHR ligands and inducers; indole 3- carboxaldehyde is an AHR ligand (Vyhlídalová et al., 2020) with selective benefit in epithelial cell proliferation rather than intestinal barrier function in piglets (Zhang, Huang et al., 2022). This raises the possibility that different activators/inducers may augment receptor bias regarding which phenotypes might be most affected. In this context, in a mouse model of immune cancer checkpoint–induced colitis, indole 3- carboxaldehyde alleviated colitis without affecting the antitumor efficacy of the immune cancer checkpoint (Renga et al., 2022). Enteric formulated indole 3-carboxaldehyde has been characterized for therapeutic use in murine metabolic syndrome (Puccetti et al., 2021). However, microbial metabolites, specifically indoles, can also drive cancer growth via AHR (Hezaveh et al., 2022). Ellagitannin-containing foods are partially converted to urolithin A, an AHR ligand (Shen et al., 2021). Urolithin A analog, UAS03, is efficient in reducing colonic inflammation and enhancing barrier function in vivo (Singh et al., 2019). It is important to note that not all microbial metabolite ligands of AHR will result in a typical phenotype (indole), and indole 3-carboxaldehyde (AHR ligand) protects against *E.coli*-induced endometritis in dysbiotic mice. Still, indole propionic acid does not (Zhao, Bao et al., 2022). Yet it is abundantly clear that in the intestines, IPA protects from inflammation (Konopelski and Mogilnicka, 2022). Thus, context is a crucial issue when evaluating metabolites as XR ligands.

Farnesoid X Receptor. More recently, intestinal commensal fungi, specifically Penicillium oxalicum SL2 produce metabolites that are ligands of FXR [e.g., (6R)3,7-dimethyl-6,7-dihydroxy-2(Z)-octanoic acid] (Zhao, Luan et al., 2022). Novel amino acid conjugations of host bile acids producing phenylalanocholic acid, tyrosocholic acid, and leucocholic acid have been described as novel FXR agonists. Still, they are enriched in patients with inflammatory bowel disease (Quinn et al., 2020). Newer computational models for ligand docking and binding have been published that could aid in biomimicry and synthesis of new microbial mimics (Jiang et al., 2021). Isoform- or tissue-specific ligands might tease out beneficial functions from nonbeneficial ones (van Zutphen et al., 2019; Ramos Pittol et al., 2020). Microbial bile acids may target receptors beyond FXR and PXR, as a recent study shows that NR4A1 (NUR77) is targeted by isoallo-lithocholic acid, which enhances T_{reg} function (Li, Hang et al., 2021).

Constitutive Androstane Receptor. New observations for the CAR in the intestines show that CAR acts within T cells in the small intestine to detoxify bile acids and diminish inflammation (Chen, Huang et al., 2021). However, to date, no microbial metabolites have been found as ligands to CAR. For the other receptors, LXR, PXR, PPAR, and RXR, there need to be further discovery efforts on biomimicry.

Current Challenges and Knowledge Gaps

The current challenge is to address the true impact of microbial metabolites on NR targets. First, we need to look at all 48 human receptors. Context-specific approaches are required to validate receptor-ligand relationships. In general, the microbial metabolites would be weak ligands of a given receptor; however, chemical mimics may be designed to improve potency based on their interactions with the receptor. Modest potency mimics may suffice in conditions where the chemical mimic may induce receptor abundance or be combined with microbial metabolites that function as such. In this current challenge, a better understanding of NR crosstalk would help to elucidate microbial metabolite effects on overall phenotype. For example, it is now established that there is a fine cross-sharing of promoter occupancy by multiple NR(s) such that the absence of one or more receptors could be partially compensated for by the presence of other receptors (Pascussi et al., 2004; Kumar et al., 2010; Zhai et al., 2010; Oladimeji et al., 2016; Pavek 2016; Bwayi et al., 2022). Suppose potency differences exist in activating the different NRs by a given microbial metabolite(s). In that case, the receptor interplay could have profound effects on the final phenotype of the host.

Second, we need to characterize crystal structures of microbial metabolites bound to xenobiotic receptors. This is not an easy task as many of the metabolites have significant solubility issues. More innovative approaches toward crystal structure determination would help move the field forward (Delfosse et al., 2021). It is also possible that weak ligands will not be amenable to structural resolution when bound to receptors.

Third, we need to define a system's view of how different microbial metabolites interact with a given xenobiotic receptor, for example, by performing synergy or antagonist studies of a combinatorial effect of different indole metabolites on a given xenobiotic receptor to determine what may result in synergy, additivity, or antagonism.

Fourth, we must characterize concentration-dependent effects of a microbial metabolite on different proteins/enzymes and receptor systems and present a hierarchical receptor structure that informs the scientific community of how the metabolite might function in vivo. For example, microbial metabolites also bind G protein-coupled receptors and interact with histone-modifying enzymes (e.g., short-chain fatty acids). In a system's view, this knowledge should ideally be combined with other effects the metabolite may have on other receptor systems (e.g., AHR). There is also a paucity of knowledge regarding the alternatively spliced isoforms of each NR. For example, PXR has at least three isoforms with variable expression across tissues and at least one isoform with dominant negative function (Tompkins et al., 2008; Lin et al., 2009; Breuker et al., 2014; Brewer and Chen, 2016). Thus, knowing which isoforms are targeted by the metabolite and in which tissues these interactions dominate would be a critical knowledge gap to cover.

Fifth, we need to assess whether specific diets or medications could alter metabolites significantly and how that affects receptor physiology and phenotypes in an intact host. This is a very challenging aspect of discovery. It is now established that in the human diet, for example, fiber or fat consumption markedly changes the microbial structure and the metabolome in the feces and gut mucosa (Claesson et al., 2012; Wan et al., 2019; Dahl et al., 2020; Tanes et al., 2021). The use of medications significantly modulates the fecal microbiome and its metabolome (Weersma et al., 2020; Kumari et al., 2022). Additionally, variability introduced by ethnicity and geography also impacts a healthy gut microbiome (Shanahan et al., 2021). Carefully controlled human studies are required from which fecal metabolomes are tested against various XRs. These should also be modeled in appropriate animal models of the disease where possible.

Sixth, we should assess for xenobiotic receptor selectivity and categorize single versus dual versus multireceptor engaging mimics, noting which receptors, when engaged, are prone to be off-target and contribute to toxicity of the compound.

Seventh, we must define ligands/mimics with other binding modes, especially orthosteric versus allosteric antagonism of receptors (Biswas et al., 2009; Chai et al., 2020).

Finally, we need to understand how microbial metabolite mimics may be developed in the context of the known fact that since these XRs are expressed in both the intestines and liver, there is a potential for unpredictable drug–drug or metabolic adverse interactions. For example, a potent PXR ligand could induce high blood cholesterol (Meng et al., 2019; Sui et al., 2021) or even drug interactions with coadministered drugs by the induction of cytochrome [CYP enzymes and phase III transporters (e.g., MDR1)]. One strategy might be to consider compounds with colonic delivery to bypass systemic delivery via absorption in the small intestines. This could also bypass drug–drug effects that in the intestines might most likely occur during small intestinal CYP and transporter induction. However, this aspect requires proof-of-concept and validation before they are adopted within the therapeutic platform.

Perspective on Future Directions

Discovery of Natural Microbial Metabolite Agonists of XRs. With the advent of pulldown approaches and insights into deconvolution of metabolites by mass spectrometry (Kim et al., 2011), the Krause laboratory has had significant success in delineating novel ligands to XRs such as PPARα (Liu et al., 2022). A similar effort is needed to capture fecal and tissue homogenates from rodents and humans, especially using a solid phase microextraction (Huang et al., 2019; Sajid et al., 2019; Kataoka, 2021). Mining the literature for new microbially produced ligands (e.g., N-methylserotonin) (Han et al., 2022), could also be screened for ligand activation across multiple xenobiotic receptors. Careful and context-driven applications of these metabolites should be fully assessed. In addition, defining all the modifications of the metabolite in the host would be relevant to how host metabolism (e.g., via CYP450s) alters how the metabolite interacts with a particular NR. For example, baicalein efficiently interacts with PXR, but its glucuronide metabolite is a weak interactor (Dou et al., 2012). Similarly, microbial metabolites in a host could be heavily modified by host metabolism resulting in mixtures of the parent metabolite and its metabolism by-products. In addition, microbial metabolites could interact with their cognate receptors (e.g., mouse PXR ligand pregnenolone carbonitrile does not activate human PXR, and similarly, rifampicin, a human PXR ligand does not activate mouse PXR). So species-specific interaction rodent models should be employed to study the in vivo aspects of metabolite–XR interactions and phenotypes.

Discovery of Natural Microbial Metabolite Antagonists of XRs. To date, very few microbial metabolite antagonists of XRs have been described. One study shows that mice treated with tempol have reduced *Lactobacillus* and bile salt hydrolase in the gut, and this leads to an increase in Tauro-β-muricholic acid, which is an FXR antagonist (Li, Jiang et al., 2013). Indeed, several other bile acid conjugates, Tauro-conjugated beta, and alpha-muricholic acids have also been identified as FXR antagonists (Sayin et al., 2013; Degirolamo et al., 2014; Gonzalez et al., 2016). Other examples include combinatorial concentrations of indoles that, in some combinations, act to antagonize the AHR (Jin et al., 2014). Emphasis must be placed on finding novel natural microbial metabolites as antagonists for XRs. As previously mentioned, mining the literature for novel microbially produced ligands with well-defined host phenotypes (e.g., imidazole propionate) (Koh et al., 2018) can guide the assessment of ligand-XR interactions.

Discovery of Physiologically Relevant Interactions of Metabolites on Receptor Systems. A more comprehensive review of the different receptor systems that are engaged by microbial metabolites has been published (Zheng et al., 2022). Here we call for a detailed analysis of receptor dynamics using combinatorial concentrations of microbial metabolites that may be present in a context-dependent manner in a host. There could be significant concentration dependencies of different metabolites on different receptors, and knowledge of how this could be integrated would significantly advance our understanding of host–microbiome relationships.

Systems Study of Multiple Metabolite–XR Interactions on Host Physiology or Pathophysiology. In an intact host, multiple microbial metabolites are contextually present and can drive phenotypes. For example, tryptophan loading increases indole metabolites of tryptophan (Wikoff et al., 2009), and in this manner, diet could influence the metabolite repertoire considerably. In the context of host pathophysiology, during intestinal inflammation, indole metabolites decrease (Alexeev et al., 2018), and depending on the diet, these levels could replete or vary considerably (Li, Illés et al., 2021). The net outcome could vary on several levels, one of which is dietary constituents. In the future, more controlled systematic studies of metabolite XR interactions are needed as they relate to specific host physiologies or pathophysiological conditions.

Conclusions

We are honored to contribute a minireview to the Xenobiotic Receptors special section in honor of *Drug Metabolism and Disposition*'s 50th anniversary. The 50th anniversary celebrates Professor Wen Xie's contributions to the field and congratulates him on the well-deserved honor of being the recipient of the Richard Okita Early Career Award in Drug Metabolism and Disposition. Following Professor Xie's landmark paper in *Nature* describing the first humanized steroid and xenobiotic receptor mice in 2000 (Xie et al., 2000), the entire orphan NR field, and acknowledging the seminal contribution of other investigators and receptor systems, has exploded with discoveries and novel pathways regulated by these receptors. We anxiously await new treatment paradigms built on a new fund of knowledge of how these xenobiotic receptors contextually contribute to disease.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Mani, Li, Dvořák.

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