Nuclear Receptor Research
vol. 4 (2017), Article ID 101316, 10 pages
doi:10.11131/2017/101316

AgiAl Publishing House
http://www.agialpress.com/

Review Article

Gut Microbiota and Host Nuclear Receptors Signalling

Harmit S. Ranhotra

Department of Biochemistry, St. Edmund's College, Shillong 793 003, India

Abstract. Systemic homeostasis in animals is maintained by a network of complex signalling pathways involving several kinds of endogenous molecules/metabolites. Over the years, the role of microbiota present in the digestive tract in animal physiology has been under focus and path-breaking findings have been reported. It seems that the gut microbiota has an influence in perhaps almost all the physiological functions, including the central nervous system in animals. The means by which the microbiota impinges control on the host system biology is manifold and complex. However, one of the mechanisms involve microbiota-derived metabolites that functions as ligands to modulate host tissue gene expression via the nuclear receptors (NRs), which is a novel way of exerting control over the host physiology. Few of the host NRs, such as the pregnane X receptor (PXR), farnesoid X receptor (FXR) and peroxisome-proliferator activated receptors (PPARs) gene transcriptional activities have been demonstrated to be modulated by the binding of microbial-secreted metabolites acting as ligands. Such interactions control vital functions in the host such as intestinal epithelial barrier protection, immune tolerance and anti-inflammatory responses. In this article, recent important findings in understanding gut microbiota-derived metabolites and select host NRs signalling will be briefly reviewed.

Keywords: Gut, intestinal epithelial cells, microbiota, metabolites, nuclear receptors.

Corresponding Author
Harmit S. Ranhotra
harmitran@gmail.com

Editor
Changcheng Zhou

Dates
Received 10 October 2017
Accepted 20 November 2017

1. Introduction

Animals, including humans require the integrative functions of various physiological systems in the body in order to provide optimal conditions for growth and development and ultimately survival. Physiological systems consist of the various organs and tissues working in tandem to achieve desired results. However, the enormous microbiota mass (~1 kg) found in the mucosal surface of the human colon is also seen as another active 'endocrine organ' of the body [1]. The gut microbiota is an amalgamation of diverse species of microbes including, bacteria, fungi, archaea and viruses, with the bacterial population (100×10^{12}) dominating the microbial family [2, 3]. The gut bacteria exhibits huge phylogenetic diversity and dynamic composition amongst individuals and is influenced by age and various environmental conditions [4]. The relationship between the host and microbiota exhibit mutualism which ultimately contributes to dual survival. The microbiota influences several functions in the host including gastrointestinal physiology and shapes both innate and adaptive immunity [4]. Pathways and mechanisms whereby such functions are regulated, however, are less understood. Findings over the last few years revealed that the gut bacterial counterpart secretes metabolites that have modulatory effect and is one of the novel and effective means of controlling various host physiology [5, 6]. A multitude

of substrates are derived from the diet as well as from host metabolism which the gut microbiota processes and modifies to generate the active metabolites. In turn some of these metabolites have specific effect on the host molecular events through various mechanisms, including ones mediated by members of the nuclear receptors (NRs) superfamily of transcription factors [7]. Microbial metabolites serve as robust signals in the proper functioning and maintenance of the intestinal epithelial cells (IECs) integrity, including the immunocytes leading to immune tolerance and anti-inflammatory responses amongst various other benefits [7]. However, most of the gut microbial metabolites are unidentified and even majority of the known ones are not fully characterized yet. It is estimated that roughly 10% of gut microbial-derived metabolites are present in the mammalian blood circulation [5–7]. Metabolites secreted by the gut microbiota can originate directly from the breakdown of dietary components, from microbial *de novo* biosynthesis and also from host-derived molecules that are transformed by the microbiota. Here an attempt has been made to review the new findings with respect to microbiota-secreted metabolites and its modulation of the host NRs signalling pathways.

2. Microbial Metabolites and Farnesoid X Receptor (FXR)

One of the ways by which the secreted microbial metabolites exert their effect is by interacting with the target host nuclear receptors (NRs) that lead to regulated gene expression and consequent biologic effects [7]. NRs represent a superfamily of eukaryotic ligand-activated transcription factors with widespread role in biological processes [8]. Many of the secreted microbial metabolites acting as ligands diffuse inside the host intestinal cells and interact with the specific NRs. This interactive system provides a direct influence of the microbiota on the host physiology which can have control on the health and disease status of individuals (Figure 1). Moreover, it is now well-known that changes in the microbiota composition and diversity impact the host physiology and is often associated with the onset and progression of diseases such as obesity, cancer, atherosclerosis and inflammatory bowel diseases (IBDs) [9].

Bile acids (BAs) made by the liver are stored in the gall bladder in animals and are meant to act as detergent that aid in the digestion and absorption of lipids in the small intestine. However, a fraction of the secreted BAs undergo biotransformation (from primary BAs to secondary BAs, such as cholic acid into deoxycholic acid) by the resident gut bacteria which then act as ligands for FXR (NR1H4), also known as bile acid receptor and regulate its gene transcriptional activity [10]. BAs-activated FXR regulate general metabolism in the host such as lipid, glucose metabolism and hepatic autophagy, including communication between the gut microbial communities [11]. An interesting study by Li *et al* showed that an antioxidant tempol remodels the gut microbiota by specifically decreasing *Lactobacillus* population and reduces obesity in mice with concomitant increase in the level of intestinal BA called tauro-β-muricholic acid (T-β-MCA), a FXR antagonist [12]. The finding also showed that tempol did not reduce obesity in FXR null mice indicating that T-β-MCA-induced antagonism of intestinal FXR activity mediates the anti-obesity effect. A related study in mice subjected to high-fat diet (HFD)-induced non-alcoholic fatty liver disease (NAFLD) showed that upon treatment with tempol and consequent increase in intestinal Tβ-MCA level and FXR inhibition led to reduced hepatic triglyceride accumulation due to lesser circulating ceramide level [13]. Repression of ceramide expression genes as a result of FXR inhibition led to reduced hepatic lipogenesis. Moreover,

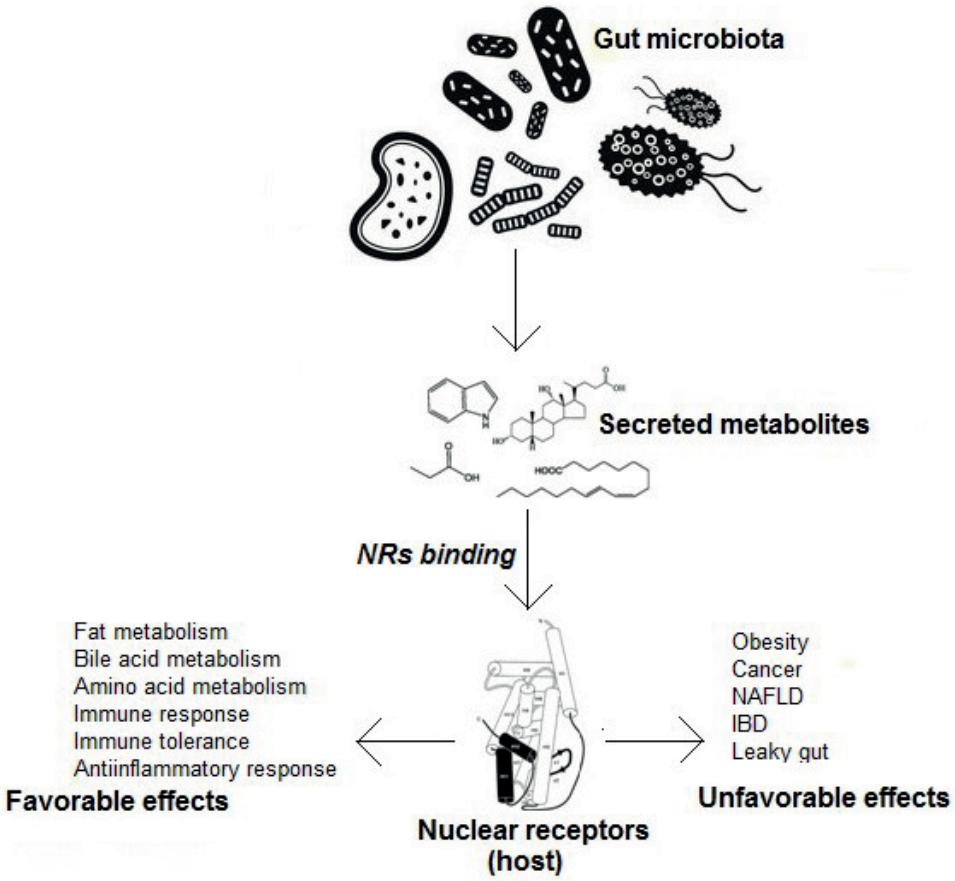


Figure 1: A schematic picture showing gut microbiota-secreted metabolites binding to host nuclear receptor (NRs) and its modulation of various functions (favourable effects) by regulating specific gene expression. On the other hand, dysbiosis and alteration in the type of secreted metabolites in the gut can give rise to unfavourable effects in the form of disease onset in the host.

FXR null mice on HFD showed reduced hepatic triglyceride content and that administration of C16:0 ceramide to tempol-treated HFD mice stimulated NAFLD [13]. These finding, though preliminary, demonstrate a link between gut microbiota-derived BAs and down regulation of FXR transcriptional activity in the control of obesity and NAFLD. In the future, it might be possible to alter the gut microbiota composition by either drug or diet targeting in order to modulate BAs composition that may act as agonists or antagonists of FXR that could be helpful in human health and disease.

The expression profile of genes involved in host bile acid synthesis, conjugation, and re-absorption is altered by the resident gut microbiota. Regulation of bile acid synthesis and homeostasis is known to be controlled by FXR [14, 15]. Investigation by Sinal *et al* has shown that the expression of FXR is upregulated in the ileum by a gut microbiota along with its target gene *Shp* and *Fgf15* in normal mice compared to germ free mice [14]. Moreover, the upregulation of FXR and its target was only observed in the ileum and not in the liver indicating a role played by the gut bacteria in regulation of FXR expression in the ileum. In addition, microbial diversity in the gut controls bile acids level in the small and large intestine. In fact BAs composition in different organs, including the blood circulation is markedly different in control and germ-free animals [15]. In an interesting study by Parseus *et al*, it was observed that in mice, the gut microbiota stimulated HFD-induced obesity via the FXR-mediated action [16]. $Fxr^{-/-}$ mice fed on a HFD

for 10 weeks failed to develop obesity in contrast to conventionally-raised (CONV-R) wild-type mice which gained significantly more weight than germ-free (GF) wild-type mice. Interestingly, the secondary BA profiles and the faecal microbiota composition were altered between $Fxr^{-/-}$ and CONV-R wild-type mice. Thus it seems plausible that the gut microbiota promotes diet-induced obesity via BAs activation of FXR, and that FXR may contribute to increased adiposity by modulating the composition of the gut microbiota. An obvious question arises with regard to the proportion of secondary BAs availability in the gut with respect to the primary BAs. Since secondary BAs are exclusively generated by the microbiota, however, some of the primary BAs also function as FXR agonists. Moreover, it can only be hypothesized as to what could happen during significant alterations in the level either of the two types of bile acids in the gut with respect to FXR functions in the host.

3. Microbial Metabolites and Aryl Hydrocarbon Receptor (AHR)

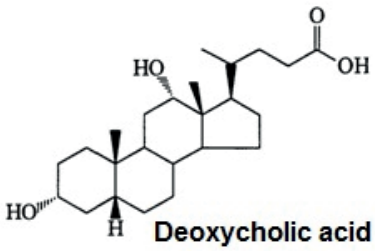
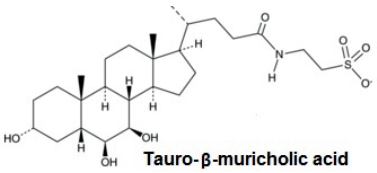
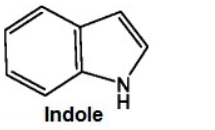
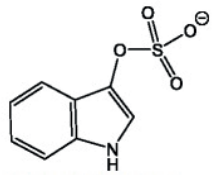
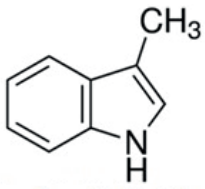
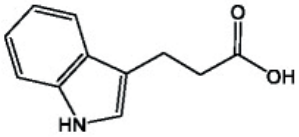
Dietary tryptophan metabolism by resident gut microbiota, particularly *Lactobacilli* spp. yield indole, an aromatic bicyclic molecule and its metabolites that are potent agonists of the host aryl hydrocarbon receptor (AHR). AHR is a cytoplasmic, ligand-activated receptor expressed in many cell types, including intestinal epithelial cells (IECs), immunocytes and has crucial roles in maintenance of intestinal mucosal homeostasis and immune response [17]. By applying an integrated *in vitro* ligand binding, qPCR, protein-DNA interaction and ligand structure activity of the ligand-binding domain (LBD) of AHR confirmed that indole and 3-methyl indole is selective human-AHR agonist [17]. However, these metabolites failed to significantly activate mice AHR probably due to a bimolecular (2:1) stoichiometry between indole and the LBD of human AHR. Moreover, cell lines study showed activation of several AHR target gene expression such as *Cyp1a1* and *Cyp1b1* upon binding of indole to human AHR [17, 18]. In an interesting report by Rothhammer *et al* it was demonstrated that interferon type 1 (IFN-1) along with tryptophan metabolites indole, indoxyl-3-sulfate, indole-3-propionic acid (IPA) and indole-3-aldehyde exert activation of the AHR in the astrocytes to suppress inflammation of the central nervous system in mice [19]. Interestingly, absence or deficiency of AHR and its microbial-derived ligands alter gut microbiota composition and turnover of IECs [20]. In fact, microbiota-derived indole and its derivatives through binding to AHR stimulate specific innate lymphoid cell (ILC) populations particularly the group 3 ILC (ILC3s) [21]. ILC3 cells through interleukin 22 are important in antimicrobial peptides (AMPs) synthesis and secretion that restrict gut pathogen survival [21]. In another study on the microbiota-derived metabolites from the mouse gut, 5-hydroxy-L-tryptophan and salicylic acid were identified as potential activators of AHR by mass spectrometric methods [22]. However, it remains to know how these two metabolites affect gut homeostasis.

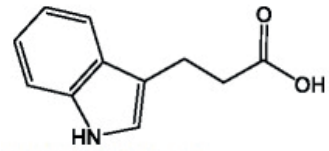
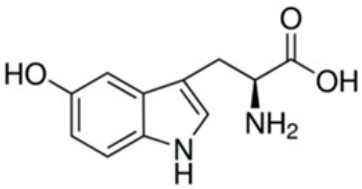
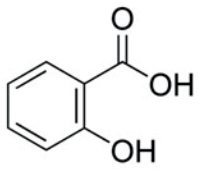
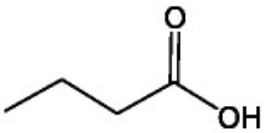
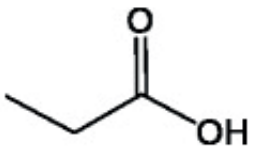
Over the years it has been thought that the AHR signalling has to be tightly regulated as uncontrolled or prolonged ligand activation (due to reduced ligand metabolic clearance) or constitutive AHR activation may compromise gut homeostasis [23]. AHR signalling in the host is controlled by cytochrome P450 enzymes (CYP) such as CYP1A and CYP1B sub-families of enzymes because they metabolize AHR ligands and attenuate its activation and downstream signalling. On the other hand, CYP1A and CYP1B gene expression is controlled by AHR

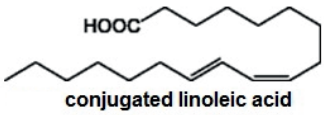
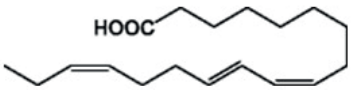
itself. In a recent report, it was observed that CYP1 enzymes also control cellular AHR ligand availability [24]. Dysregulated CYP1A1 gene expression in mice leads to significant reduction in the cellular level of AHR agonists, whereas a constitutive expression in the IECs led to the disappearance of AHR-dependent ILC3s and T helper 17 cells which increases the chance of infection of the intestine [24]. This shows that the immune cells are dependent on optimal AHR signalling for their specific roles in the intestine. Gut microbiota metabolizes dietary polysaccharides, mainly cellulose by fermentation to generate short-chain fatty acids (SCFAs) such as acetate, butyrate and propionate. Butyrate and propionate, but not acetate control AHR gene expression in HT-29 cells [25]. Also, SCFA-activated AHR has a control over the gut microbial composition in $AhR^{+/+}$ (wild-type) and $AhR^{-/-}$ (knock-out) mice. SCFAs were also demonstrated to modulate AHR activity in an indirect manner via the G-protein coupled receptors (GPCRs), which uses SCFAs as ligands [25]. Few diseases are known to occur and progress due to breakdown in gut homeostasis as a result of compromised microbiota and AHR signalling. A recent report by Lamas *et al* demonstrated relationship between gut microbiota and the host caspase recruitment domain family member 9 (CARD9) [26]. CARD9 is a known susceptible gene for inflammatory bowel disease (IBD) which has a role in immunity against microorganisms. Microbiota from Card9(-/-) null mice are unable to metabolize tryptophan into indoles that serves as AHR agonists. Moreover, it was observed that gut inflammation was reduced after introduction of three *Lactobacillus* strains that metabolize tryptophan in mice. In individuals with IBD, decreased production of AHR ligands was observed in microbiota, particularly those with CARD9 risk alleles associated with IBD [26]. Collectively, these studies indicate a strong regulatory influence of the AHR ligands on host cells, including the immune cells associated with gut immune homeostasis. Breakdown of AHR signalling in the intestinal cells may lead to inflammatory reactions and immuno-pathologies of the gut.

At present, limited number of NRs has been demonstrated to have a direct role in acting as a ligand-binding protein for the microbiota-secreted metabolites in the gut [Table 1]. As mentioned earlier, butyrate generated by the gut microbiota can act as peroxisome proliferator-activated receptor-γ (PPAR-γ; NR1C3) agonist [27]. In a recent finding, propionate secreted by gut bacteria also has been shown to be an activator of PPAR-γ [28]. PPAR-γ is a known anti-inflammatory mediator that attenuates several pro-inflammatory signalling pathways stimulated by transcription factors such as NF-κB and AP-1. Hence butyrate and propionate-mediated activation of PPAR-γ gene transcriptional activity could have a protective role in prevention of gut inflammation and regulation of immune tolerance [29]. Also, accumulated evidences suggest presence of specific bacterial strains, though not identified in the gut which influences PPAR-γ gene regulatory activity [30]. The gut microbial metabolism of dietary tryptophan yield an indole derivative called indole 3-propionate (IPA) which exhibit high affinity binding to its cognate pregnane X receptor (PXR; NR1I2) in the IECs as investigated by Venkatesh *et al* few years back [31]. The mice gut bacterium *Clostridium sporogenes* secreted IPA has anti-inflammatory and barrier protection role in the intestine mediated via the PXR. Moreover, *Nr1i2*$^{-/-}$ mice show compromised epithelial barrier protection in the gut indicating the important role of this receptor in maintaining barrier function in the host [32]. Although other indole derivatives such as indoxyl sulfate and indole-3-acetate are also secreted by the gut bacteria, however, apart from IPA, data supporting activation of intestinal PXR by them is lacking.

Table 1: Select gut bacteria-secreted metabolites and their target host nuclear receptors.

Gut bacterial metabolites	Bacterial phyla/ genera/species	Target nuclear receptors
 Deoxycholic acid	*Clostridium*, *Eubacterium*	Farnesoid X receptor (FXR)
 Tauro-β-muricholic acid	*Lactobacillus, Clostridium, Bacteroidetes*	FXR
 Indole  Indoxyl 3-sulfate	*Bacteroides fragilis, Parabacteroides distasonis, Clostridium bartlettii, Lactobacillus, Bifidobacterium longum*	Aryl hydrocarbon receptor (AHR)
 3-methyl indole	*Lactobacillus, Bacteroidetes*	AHR
 Indole 3-propionic acid	*Clostridium sporogenes*	Pregnane X receptor (PXR)

Gut bacterial metabolites	Bacterial phyla/ genera/species	Target nuclear receptors
 Indole 3-aldehyde	*Lactobacillus*	AHR
 5-Hydroxy-L-tryptophan  Salicylic acid	*Proteobacteria, Firmicutes, Actinobacteria*	AHR
 Butyrate	*Ruminococcaceae, Lachnospiraceae, Bacteroidetes*	Peroxisome-proliferator activated receptor-gamma(PPAR-γ)
 Propionate	*Escherichia coli, Bacteroidetes, Propionibacterium*	PPAR-γ

Gut bacterial metabolites	Bacterial phyla/ genera/species	Target nuclear receptors
 conjugated linoleic acid	*Bifidobacteria, Faecalibacterium prausnitzii, Propionibacterium, Lachnospiraceae, Lactobacillus*	PPAR-α, PPAR-γ
 conjugated linolenic acid		

4. Conclusion

The gut microbiota is a complex, dynamic and important constituent of our body exhibiting mutualism and has varied impact on our physiological system culminating in optimal health. Few of the gut bacterial species have been demonstrated to secrete metabolites that have significant effects on intestinal cell homeostasis and innate and adaptive immunity. The microbial-secreted metabolites in the gut include SCFAs, indole derivatives and secondary bile acids which act as natural ligands for the host NRs such as FXR, AHR, PXR and PPARγ. Such interactions have important consequences in providing intestinal epithelial barrier protection and anti-inflammatory responses. Dysbiosis in the microbial populations in the gut can have unfavourable outcome for the host in the form of disease onset such as IBDs, cancer, diabetes and obesity. Presently, limited numbers of metabolites synthesized and secreted by the gut microbiota are known and characterized that influence host biology through the nuclear receptors. An important aspect with respect to this is the available concentration of such metabolites in the gut and the mechanism and regulatory features by which they enter into the IECs to modulate the NRs. Also, it is not sure as to what could be the approximate number of secreted metabolites present in the gut and what novel pathways they probably utilize to interact with the host. Apart from affecting the host physiology itself, metabolites secreted by one microbial species most likely shall also influence other gut microbial species in variable forms which makes the entire microbiome immensely complex and dynamic [33]. Moreover, it is visualized that microbial metabolites also influence other microbial communities across taxa in the gut by signalling pathways that probably may have a role in maintaining their optimal population which benefits the host. In conclusion, the future is no doubt extremely bright in this area of research, but the challenge remains knowing the exact numbers of different microbiota-secreted metabolites in the host gut and also the microbial genera and species. More precisely, finding out the total numbers and characterization of these metabolites which actually modulate NRs activity, including the target genes in the host may pay the dividend in finding out their roles in host physiology as well as in several pathologies.

Competing Interests

The author declares no competing interests.

Acknowledgements

I am thankful to the Department of Biochemistry, St. Edmund's College, Shillong, India, for providing all the support in writing this review.

References

[1] I. I. Ivanov and K. Honda, "Intestinal commensal microbes as immune modulators," *Cell Host & Microbe*, vol. 12, no. 4, pp. 496–508, 2012.

[2] N. R. West and F. Powrie, "Immunotherapy not working? Check your microbiota," *Cancer Cell*, vol. 28, no. 6, pp. 687–689, 2015.

[3] E. K. Costello, C. L. Lauber, M. Hamady, N. Fierer, J. I. Gordon, and R. Knight, "Bacterial community variation in human body habitats across space and time," *Science*, vol. 326, no. 5960, pp. 1694–1697, 2009.

[4] J. C. Clemente, L. K. Ursell, L. W. Parfrey, and R. Knight, "The impact of the gut microbiota on human health: an integrative view," *Cell*, vol. 148, no. 6, pp. 1258–1270, 2012.

[5] J. Cheng, Y. M. Shah, and F. J. Gonzalez, "Pregnane X receptor as a target for treatment of inflammatory bowel disorders," *Trends in Pharmacological Sciences*, vol. 33, no. 6, pp. 323–330, 2012.

[6] V. Arulampalam, G. Greicius, and S. Pettersson, "The long and winding road to gut homeostasis," *Current Opinion in Gastroenterology*, vol. 22, no. 4, pp. 349–353, 2006.

[7] T. S. Postler and S. Ghosh, "Understanding the Holobiont: How Microbial Metabolites Affect Human Health and Shape the Immune System," *Cell Metabolism*, vol. 26, no. 1, pp. 110–130, 2017.

[8] T. P. Burris, L. A. Solt, Y. Wang et al., "Nuclear receptors and their selective pharmacologic modulators," *Pharmacological Reviews*, vol. 65, no. 2, pp. 710–778, 2013.

[9] A. Wahlström, S. I. Sayin, H.-U. Marschall, and F. Bäckhed, "Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism," *Cell Metabolism*, vol. 24, no. 1, pp. 41–50, 2016.

[10] S. Fiorucci and E. Distrutti, "Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders," *Trends in Molecular Medicine*, vol. 21, no. 11, pp. 702–714, 2015.

[11] Y.-F. Nie, J. Hu, and X.-H. Yan, "Cross-talk between bile acids and intestinal microbiota in host metabolism and health," *Journal of Zhejiang University SCIENCE B*, vol. 16, no. 6, pp. 436–446, 2015.

[12] F. Li, C. Jiang, K. W. Krausz et al., "Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity," *Nature Communications*, vol. 4, article no. 2384, 2013.

[13] C. Jiang, C. Xie, F. Li et al., "Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease," *The Journal of Clinical Investigation*, vol. 125, no. 1, pp. 386–402, 2015.

[14] C. J. Sinal, M. Tohkin, M. Miyata, J. M. Ward, G. Lambert, and F. J. Gonzalez, "Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis," *Cell*, vol. 102, no. 6, pp. 731–744, 2000.

[15] S. I. Sayin, A. Wahlström, J. Felin et al., "Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist," *Cell Metabolism*, vol. 17, no. 2, pp. 225–235, 2013.

[16] A. Parséus, N. Sommer, F. Sommer et al., "Microbiota-induced obesity requires farnesoid X receptor," *Gut*, vol. 66, no. 3, pp. 429–437, 2017.

[17] T. D. Hubbard, I. A. Murray, W. H. Bisson et al., "Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles," *Scientific Reports*, vol. 5, Article ID 12689, 2015.

[18] U.-H. Jin, S.-O. Lee, G. Sridharan et al., "Microbiome-derived tryptophan metabolites and their aryl hydrocarbon receptor-dependent agonist and antagonist activities," *Molecular Pharmacology*, vol. 85, no. 5, pp. 777–788, 2014.

[19] V. Rothhammer, I. D. Mascanfroni, L. Bunse et al., "Type i interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor," *Nature Medicine*, vol. 22, no. 6, pp. 586–597, 2016.

[20] Y. Li, S. Innocentin, D. R. Withers et al., "Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation," *Cell*, vol. 147, no. 3, pp. 629–640, 2011.

[21] T. Zelante, R. Iannitti, C. Cunha et al., "Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22," *Immunity*, vol. 39, no. 2, pp. 372–385, 2013.

[22] G. V. Sridharan, K. Choi, C. Klemashevich et al., "Prediction and quantification of bioactive microbiota metabolites in the mouse gut," *Nature Communications*, vol. 5, article no. 6492, 2014.

[23] P. Andersson, J. McGuire, C. Rubio et al., "A constitutively active dioxin/aryl hydrocarbon receptor induces stomach tumors," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 99, no. 15, pp. 9990–9995, 2002.

[24] C. Schiering, E. Wincent, A. Metidji et al., "Feedback control of AHR signalling regulates intestinal immunity," *Nature*, vol. 542, no. 7640, pp. 242–245, 2017.

[25] A. Korecka, A. Dona, S. Lahiri et al., "Bidirectional communication between the Aryl hydrocarbon Receptor (AhR) and the microbiome tunes host metabolism," *npj Biofilms and Microbiomes*, vol. 2, no. 1, 2016.

[26] B. Lamas, M. L. Richard, and V. Leducq, "CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands," *Nature Medicine*, vol. 22, no. 6, pp. 598–605, 2016.

[27] S. Alex, K. Lange, T. Amolo et al., "Short-chain fatty acids stimulate angiopoietin-like 4 synthesis in human colon adenocarcinoma cells by activating peroxisome proliferator-activated receptor γ," *Molecular and Cellular Biology*, vol. 33, no. 7, pp. 1303–1316, 2013.

[28] M. Nepelska, T. De Wouters, E. Jacouton et al., "Commensal gut bacteria modulate phosphorylation-dependent PPARλ transcriptional activity in human intestinal epithelial cells," *Scientific Reports*, vol. 7, Article ID 43199, 2017.

[29] M. Viladomiu, R. Hontecillas, L. Yuan, P. Lu, and J. Bassaganya-Riera, "Nutritional protective mechanisms against gut inflammation," *The Journal of Nutritional Biochemistry*, vol. 24, no. 6, pp. 929–939, 2013.

[30] A. Are, L. Aronsson, S. Wang et al., "Enterococcus faecalis from newborn babies regulate endogenous PPARγ activity and IL-10 levels in colonic epithelial cells," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 105, no. 6, pp. 1943–1948, 2008.

[31] M. Venkatesh, S. Mukherjee, H. Wang et al., "Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and toll-like receptor 4," *Immunity*, vol. 41, no. 2, pp. 296–310, 2014.

[32] W. Dou, J. Zhang, E. Zhang et al., "Chrysin ameliorates chemically induced colitis in the mouse through modulation of a PXR/NF-κB signaling pathway," *The Journal of Pharmacology and Experimental Therapeutics*, vol. 345, no. 3, pp. 473–482, 2013.

[33] K. L. Adair and A. E. Douglas, "Making a microbiome: the many determinants of host-associated microbial community composition," *Current Opinion in Microbiology*, vol. 35, pp. 23–29, 2017.