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MICROBIOME-HOST INTERACTIONS THROUGH THE ARYL HYDROCARBON RECEPTOR

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SUMMARY

The vertical transmission of the maternal microbiome to the new offspring sparks the development of a new microbiome that together with its new host forms a symbiotic entity. The microbial genome (biont) and the genome of the host (biont) represent two "bionts" which together represent a holobiont. The holobiont represent a functional unit with evolutionarily designed functions to secure nutritional intake, DNA replication and reproduction. It follows that virtually all organs within the holobiont respond to changes within the microbiome. The microbiome, in turn reciprocate, by influencing host genome function to support host physiology. The aryl hydrocarbon receptor (AhR) is an evolutionarily conserved receptor recognizing environmental compounds, including natural ligands some of which are derived from the microbiome. This small overview touches upon aspects of the microbiome-AhR communication to display an example of holobiont communication.

INTRODUCTION

Until very recently, evolutionary genetics focused almost exclusively on patterns of variation found within our mitochondrial and nuclear genomes. Yet, bacteria and archaea, two of the predominant kingdoms within the microbiome, were the dominant forms of life on Earth for approximately 3 billion years prior to the evolution of the animal kingdom (*Maloof* et al., 2010; *Bell* et al., 2015). Further to this point, it has become increasingly clear that the study of evolution is not complete without consideration of the microbiome. In addition to the somatic cells of the host, the entire body is a patchwork landscape home to thousands of different microbial species that number in the tens of trillions of cells. Rather than mere transient microbes, these co-resident organisms contain an immense diversity of genes that interact directly with our physiology to carry out vital functions. The awareness of these roles has resulted in a radical shift from thinking of host-associated microbes solely in terms of pathogens, to considering them essential members of host biology important for life. As such, the host-associated microbial communities serve as accessory genetic reservoirs that respond to changes in our environments and lifestyles to converge as a shared target for natural selection.

These new findings represent a paradigm shift in our current understanding of host physiology and place the microbiome into homeostasis mechanisms relevant to digestion and energy metabolism, immune development, neuro-

logical function, and infectious disease susceptibility. The two entities, the microbial genome and the host genome, form a holobiont with overlapping biological and biochemical needs which influence all aspects host physiology. Environmental changes affect both the host and its microbiome. The last two decades of genome-wide association studies has ignored the microbiome and, consequently, missed the response elicited within it. Through the use of germ-free (GF) mice, mice that are raised without exposure to any microbes, the holobiont physiology has begun to be addressed using a systems biology approach (*Nicholson* et al., 2012). This includes the ability of the host and microbiome to communicate, to maintain homeostasis and act correspondingly when exposed to assaults. Furthermore, the use of GF mice helps us to answer fundamental questions about the role of microbial evolution and ecology in broader patterns of host evolution. This mini review focuses on host microbiome interactions by discussing the AhR receptor as an example of an evolutionarily conserved signalling pathway that act as host receiver and transmitter to the microbiome within the holobiont.

A MICROBIOME RESPONDING RECEPTOR WITHIN THE HOLOBIONT; THE ARYL HYDROCARBON RECEPTOR

The aryl hydrocarbon receptor (AhR) is a cytoplasmic ligand-induced receptor originally discovered as a xenobiotic sensor mediating the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), also known as dioxin (*Denison* and *Nagy*, 2003; *Hu* et al., 2007; *Linden* et al., 2010; *Murray* et al., 2014). The metabolism of xenobiotic compounds is initiated by activation of the AhR, which then translocate to the nucleus, where it acts as a transcription factor for specific target genes, such as cytochrome P450 1A1 and cytochrome P450 1B1 (*Ma* et al., 2001; *Denison* and *Nagy*, 2003; *Diani-Moore* et al., 2010; *Linden* et al., 2010; *Opitz* et al., 2011; *Nguyen* et al., 2013; *Stockinger* et al., 2014). However, invertebrates do not have a toxic response to dioxin, and none of the currently known invertebrate AhR orthologues, including in spineless Drosophila, have dioxin binding capacity, which suggests that the ancestral role of the AhR is not specifically a toxin response (*Hahn* et al., 1997; *Hahn*, 2002). Furthermore, physiological roles of the AhR in responses to endogenous ligands have been reported in cell cycle regulation, cell differentiation, and immune responses (*Fernandez-Salguero* et al., 1995; *Benedict* et al., 2000; *Quintana* et al., 2008; *Opitz* et al., 2011; *Hao* and *Whitelaw*, 2013). A number of endogenous AhR ligands have been suggested through *in silico* research and biological testing, including tryptophan metabolites (*Denison* and *Nagry*, 2003; *Nguyen* and *Bradfield*, 2008; *Opitz* et al., 2011). Recently, our group discovered that AhR expression is attenuated in GF mice (*Korecka* et al., 2016). This finding suggests that the AhR acts as a mediator in communication between the host and the microbiome.

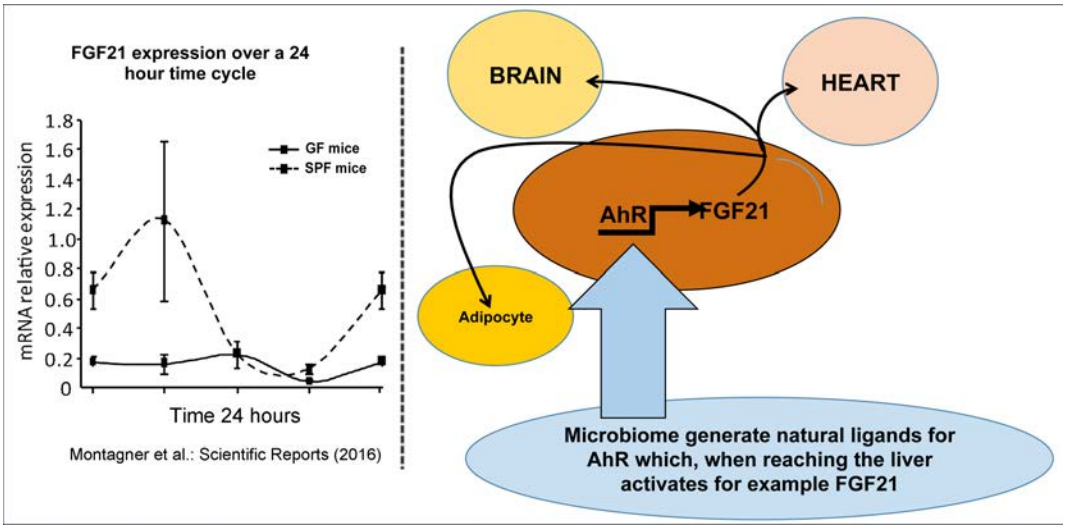

Figure 1: An example of a microbiome-host interaction in the holobiont. Microbiome mediated regulation of AhR and expression of FGF21, a liver secreted inteerorgan communicator, through te microbiome.

THE ARYL HYDROCARBON RECEPTOR RESPONDING OUTPUTS IN THE HOLOBIONT

Dioxin-activated AhR attenuates lipid metabolism via negative regulation of peroxisome proliferator-activated receptor (PPAR) (*Remillard* and *Bunce*, 2002). Dysregulation of lipid metabolism leading to hepatic steatosis and insulin resistance suggests that the AhR plays an important role in integrating exogenous and endogenous influences in lipid and energy metabolism (*Lee* et al., 2010; *Lu* et al., 2015). Findings from AhR-deficient mice show that, like GF mice (*Backhed* et al., 2007; *Rabot* et al., 2010), they are protected from high fat diet-induced obesity, hepatic steatosis, and insulin resistance (*Xu* et al., 2015).

Recently, fibroblast growth factor 21 (FGF21) was reported to be a novel target gene of the AhR. FGF21 increases lipid oxidation and ketogenesis but decreases gluconeogenesis at the gene expression level (*Badman* et al., 2007; *Inagaki* et al., 2007). As an insulin sensitizer, FGF21 boosts the metabolic benefits such as improved blood glucose levels due to increased glucose uptake in adipocytes, reduced body weight due to increased energy expenditure, and improved blood lipid profiles due to hepatic sequestration of lipid droplets (*Kharitonenkov* et al., 2005; *Coskun* et al., 2008; *Lu* and *Klaassen*, 2011). TCDD-induced AhR activation has been shown to increase FGF21 mRNA in both a dose- and time-dependent manner in mouse liver (*Lee* et al., 2010; *Lu* et al., 2015). In addition, drug-induced over-expression of human AhR in mice induces the activation of FGF21, which may then result in decreased insulin resistance (*Cheng* et al., 2014). The opposite effects were observed with the down-regulation of FGF21 – insulin insensitivity, deranged lipid profile, and liver inflammation – and can be associated with the attenuation of hepatic lipid accumulation and increased transfer of fats out of the liver in hepatocyte-tar-

geted AhR knockout (KO) (*Lu* et al., 2015).

Recent work from our lab linked the mechanism of microbiota and host communication through an AhR-dependent mechanism. We demonstrated that the AhR is differentially expressed in GF mice and that the FGF21 expression in liver is subject to regulation by the microbiome (Figure 1). This suggests a microbiome mediated signalling pathway in which microbes regulate FGF21 expression and thus its effector function as an inter-organ communicator (Figure 1). Similarly, our AhR-KO study showed that AhR regulates a set of metabolic genes in the liver, including CD36 (involved in fatty acid uptake) and Hmgcs2 (an enzyme involved in ketone body regulation) (*Korecka* et al., 2016). Similar to fast-induced adipose factor-KO mice (*Backhed* et al., 2007), AhR-KO mice gain weight as expected but do not develop insulin resistance (*Korecka* et al., 2016), suggesting that AhR could be the upstream link between microbiota-mediated signals and the host (*Korecka* et al., 2016).

Several reports have associated AhR function with the regulation of the immune system. TCDD treatment has shown that AhR has the capacity to mediate the differentiation and/or function of T cells, macrophages, and dendritic cells (*Veldhoen* et al., 2008, 2009; *Kimura* et al., 2009; *Ghandi* et al., 2010; *Quintana* et al., 2010; *Hao* and *Whitelaw*, 2013; *Nguyen* et al., 2013; *Stockinger* et al., 2014). The activation of AHR by TCDD (*Warren* et al., 2000; *Vorderstrasse* et al., 2003; *Jin* et al., 2014a) and the ablation of AhR in KO animals (*Yamada* et al., 2016) have implicated this receptor in viral immunity. We also recently reported that ablating the AhR in $CD11c^{+}$ cells perturbs the development of the intestinal epithelium and intestinal immunity (*Chng* et al., 2016). Depending on the presence of specific ligands, AhR activation has also been shown to suppress or exacerbate responses in experimental autoimmune disease models. For example, TCDD and 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) can suppress experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS) (*Quintana* et al., 2010), whereas the activation of AhR by ligands such as 6-formylindolo[3,2-b]carbazole (FICZ) exacerbates the development of EAE (*Quintana* et al., 2008, 2010; *Veldhoen* et al., 2008; *Duarte* et al., 2013). In addition, the affinity of AhR for ligands (TCDD, high affinity; FICZ, low affinity) influenced the amount of IL-17 and IL-22 protein secreted by Th17 cells (*Mezrich* et al., 2010). These findings indicate that various ligands for AhR may have different effects on host development.

MICROBIOME DERIVED NATURAL LIGANDS FOR THE ARYL HYDROCARBON RECEPTOR

Though most research on AhR has focused on man-made high affinity binding ligands and chemical pollutants, recent research has implicated important roles for an array of low affinity natural ligands produced, metabolized, or influenced by the gut microbiota. Natural ligands for AhR can be divided into three groups: host mediated, microbiota mediated, and dietary compounds.

The essential amino acid tryptophan is the major source for both host-mediated and microbiome-mediated AhR ligands. Kynurenine (KYN) is converted from tryptophan by tryptophan

2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) and is an important AhR ligand (*Mezrich* et al., 2010). Kynurenic acid (KYNA) is converted from KYN by kynurenine aminotransferase and also an important ligand (*DiNatale* et al., 2010). Our research has shown that the microbiota regulates the expression of IDO in the liver, and although IDO may play a more important role in KYN metabolism in extra-hepatic tissue (*Badawy*, 2015), these results indicate a need to analyse the role of the microbiota in KYN metabolism (*Korecka* et al., 2016).

Gut microbiota also convert tryptophan to indole, indole-3-acetate, and tryptamine, which have been identified in mouse and human intestine and work as AhR agonists and antagonists (*Jin* et al., 2014b; *Hubbard* et al., 2015). Microbial pigment virulence factors, namely the phenazines from microbes such as *Pseudomonas aeruginosa* and the naphthoquinone phthiocol from *Mycobacterium tuberculosis*, act as microbiota-mediated AhR ligands. Upon ligand binding, activation leads to virulence factor degradation and regulates cytokine and chemokine production (*Moura-Alves* et al., 2014). Short chain fatty acids, such as propionic acid and butyrate, from the microbiome are not direct ligands for AhR, but our recent data suggest that they stabilize AhR, increasing its activity in the presence of true ligands. The majority of dietary AhR ligands are produced by plants. Plant-derived compounds that act as ligands for AhR include flavonoids, stilbenes, carotenoids, and some indoles. Indole-3-carbiol (I3C) is an indole compound found in cruciferous vegetables that is converted to higher affinity AhR ligands, such as indolo-[3,2-b]-carbazole and 3,3'-diindolymethane in the acidic environment of the stomach (*Shertzer* and *Senft*, 2000).

MICROBIOME COMMUNICATING WITH THE HOST NERVOUS SYSTEM

Sudo et al. (2014) first demonstrated a possible link between the hypothalamic-pituitary-adrenal (HPA) axis and the gut microbiome. Elevated adrenocorticotropic hormone and corticosterone levels were observed in GF mice compared to specific pathogen-free (SPF) mice in early life. They also demonstrated that brain-derived neurotrophic factor (BDNF) is significantly reduced in the hippocampus and cortex of GF mice (*Sudo* et al., 2014). Later studies confirmed regulation of steady state levels of BDNF by the microbiome (*Bercik* et al., 2011; *Diaz Heijtz* et al., 2011), which plays an important role in neuroplasticity, neuron differentiation, and the maintenance and protection of neurons under stress. Many of these groups have linked changes in brain biochemistry to altered behaviours in GF mice (*Bercik* et al., 2011; *Diaz Heijtz* et al., 2011; *Sudo* et al., 2014).

Recently there have been reports that the microbiome plays an important role in the growth and function of CNS cell populations. Hippocampal neurogenesis was shown to be increased in GF mice (*Ogbonnaya* et al., 2015), which also correlated to increased volume and abnormal neuronal morphology in the hippocampi of GF mice (*Luczynski* et al., 2016). Similarly there was increased amygdala volume in GF mice with concomitant neuronal morphology (*Luczynski* et al., 2016). In contrast to this, hippocampal neuro-

genesis was shown by Möhle and colleagues to be decreased in mice treated with antibiotics (*Möhle* et al., 2016). They demonstrated that their model of antibiotic depletion lead to decreased hippocampal neurogenesis through modulation of the populations of specific immune cells (*Möhle* et al., 2016). Our group have also reported that the microbiome plays a key role in the maintenance of other synaptic proteins, including synaptophysin and PSD-95, which are reduced in the striatum of SPF mice, suggesting abnormally hyperactive synaptogenesis in the striatum of GF mice (*Diaz Heijtz* et al., 2011). The microbiome has also been implicated in the functionality of glial cells. Our group has demonstrated that the microbiota is instrumental in the development of the blood-brain barrier (BBB) (*Braniste* et al., 2014). Finally, *Hoban* et al. (2016) demonstrated that in the absence of microbiota, there is increased myelination of neurons in the pre-frontal cortex. Taken together, these early correlative findings highlight the ability of the microbiome to communicate with the host on critical aspects of host function and further underscore the necessity of a bilateral crosstalk between the microbiome and the host to generate a functional holobiont. That said, the knowledge on underlying molecular mechanisms linking the microbiome to the nervous system remains limited and is what the field needs.

THE ARYL HYDROCARBON RECEPTOR AND THE CENTRAL NERVOUS SYSTEM

Reports on the AhR in neurodevelopment are very limited. However, the AhR appears to be vital in the maintenance of some key pathways in neurodevelopment in worms. In *Caenorhabditis elegans*, *Huang* et al. (2004) demonstrated a role for AhR in neural cell fate determination, particularly for GABAergic neurons. AhR-1 is the AhR orthologue in *C. elegans*. In worms with AhR-1 mutations, two specific neurons out of the 302 total neurons have been reported to appear and act like a second pair of neurons that could be reprogrammed into the first pair of neurons by ectopic administration of AhR-1 (*Huang* et al., 2004). In addition, *Qin* et al. (2004) found that AhR-1 is responsible for the development, orientation, and axonal migration of AhR-1-expressing neurons in *C. elegans*. Taken together, these results demonstrate that AhR contributes to the cell fate determination of specific neuronal populations in worms, possibly through natural ligands and irrespective of dioxin exposure.

Dioxin toxicity studies have demonstrated that the AhR is likely to play a role in CNS development. In zebrafish, TCDD exposure was reported to reduce the total number of neurons by 30 % (*Hill* et al., 2003). In mice, dioxin toxicity studies have demonstrated a similar role for AhR in the embryonic differentiation of GABAergic neurons in the telencephalon (*Gohlke* et al., 2009) and the neurogenesis of cerebellar granule cells (*Williamson* et al., 2005). Importantly, due to the extraordinarily high binding affinity of dioxin for the AhR, emphatic conclusions regarding the physiological role of the AhR in normal development cannot be drawn from dioxin studies alone.

The AhR was also shown to play a crucial role in CNS development in studies more consistent with typical biology. The expression of a constitutively active AhR in mice retarded the

development of interneurons in the olfactory bulb (*Kimura* et al., 2016). Furthermore, in mouse primary cortical neurons, AhR activation by FICZ was also shown to increase the expression of synaptophysin and SAP102, but not PSD95 (*Hsu* et al., 2014). In functional experiments, the AhR was shown to alter hippocampal neurogenesis and contextual fear memory in mice (*Latchney* et al., 2013), as well as aggression behaviour in *C. elegans* (*Qin* et al., 2006). *Latchney* et al. (2013) demonstrated that adult AhR-KO mice and TCDD-exposed mice hippocampal-dependent memory impairment. AhR-deficient mice and TCDD-exposed mice also exhibited reduced cell proliferation, survival, and differentiation in the adult dentate gyrus. The conflicting data demonstrating both the KO and activation of AhR lead to similar outcomes, suggesting that the AhR plays a vital role in CNS homeostasis.

A DYSFUNCTIONAL HOLOBIONT IN EARLY LIFE

Autism spectrum disorder (ASD) is a neurodevelopmental illness for which evidence supports a possible link between the maternal/early postnatal microbiome and dysfunctional neurodevelopmental programming. From a human health perspective, the association between the microbiome and neurodevelopment was highlighted by evidence that people suffering from ASD also frequently present with problems related to a dysfunctional bowel with aberrant intestinal barrier function (*Rosenfeld*, 2015). Although the association remains controversial, a role for dysfunctional gut microbiome-brain axis has gained further support from the recent demonstration of different microbiome composition in children with ASD compared to age-matched controls (*Krajmalnik-Brown* et al., 2015).

A recent study demonstrated that, in an animal model of ASD, correction of the microbiota with probiotic administration of *Bacteroides fragilis* corrected biochemical and behavioural abnormalities associated with ASD (*Hsiao* et al., 2013). In this ASD mouse model, the key effector in the microbiota-gut-brain axis was the metabolome; a number of specific metabolites altered in the ASD mouse model were normalized by the treatment. Indolepyruvate, a microbially controlled molecule that is metabolized into an AhR agonist, was significantly regulated in the ASD model and by *B. fragilis* treatment (*Hsiao* et al., 2013). This metabolite is an interesting corollary to indolyl-3-acryloylglycine, which has been shown to be elevated in the urine of humans with ASD (*Bull* et al., 2003).

Epidemiological studies of Vietnamese children exposed to TCDD in the prenatal and perinatal period have demonstrated increased neurodevelopmental defects and autistic traits in children with greater exposure to TCDD (*Tran* et al., 2016). Prenatal and postnatal exposure to KYN in rats causes cognitive defects in adulthood (*Pocivavsek* et al., 2012). Although Pocivavsek and colleagues did not identify a specific mechanism underlying the association between early life KYN exposure and cognitive deficits, they did note that the treatment led to 3.4- and 2.1-fold increases in KYNA levels in the brain at postnatal days 2 and 21, respectively (*Pocivavsek* et al., 2012). Although they noted the effects of KYNA as an antagonist of the α7 nicotinic acetylcholine receptor and the N-methyl-d-aspartate receptor (*Poci-*

vavsek et al., 2012), KYNA is also an AhR ligand with a stronger binding affinity for the AhR than KYN (*DiNatale* et al., 2010), potentially implicating AhR activity in the cognitive abnormalities observed in this model. While still in its infancy, it is tempting to speculate that the AhR signalling pathway and its microbially derived natural ligands are of great interest to better understand the underlying mechanisms of Autism Spectrum Disorders.

THE HOLOBIONT AND THE BLOOD-BRAIN BARRIER

The AhR is widely expressed in the CNS (*Filbrandt* et al., 2004; *Jacob* et al., 2011). However, our understanding of the role of the AhR in neurons and supporting cells is still very limited. The BBB is vitally important in the maintenance of CNS homeostasis and its weakening has been suggested to contribute to neurodegenerative pathology. Breakdown of the BBB at the hippocampus has been correlated with cognitive impairment in humans (*Montagne* et al., 2015). Previously, our group reported that the BBB exhibits increased permeability in adult GF mice (*Braniste* et al., 2014). Monocolonization with *Clostridium tyrobutyricum* or *Bacteroides thetaiotaomicron* and treatment with sodium butyrate had rescuing effects on BBB permeability and tight junction protein expression (*Braniste* et al., 2014). One mechanism of the microbiome-mediated effects on BBB permeability appeared to be related to changes in the expression of tight junction proteins, such as occludin and claudin-5 (*Braniste* et al., 2014). A recent report demonstrated that induction of dysbiosis with a mixture of antibiotics caused alterations in the mRNA expression of tight junction proteins in the brain (*Frohlich* et al., 2016), validating, at an mRNA level, the results produced by *Braniste* et al. (2014) in a separate model of microbiome disruption.

The presence of the AhR and expression of its target genes has been shown to be significantly elevated in the micro-vessels of the brain (*Filbrandt* et al., 2004; *Dauchy* et al., 2008). Contradictory results have been reported. Via activation by TCDD, the AhR decreases the permeability of the BBB *in vivo* (*Wang* et al., 2011a,b), but increased BBB permeability was observed following exposure to 3-methylcholanthrene (*Chang* et al., 2012). Interestingly, though the increased BBB permeability reported by *Braniste* et al. (2014) has not been assessed in the context of the AhR, a recent study in keratinocytes demonstrated that ligand activation of the AhR elevates occludin and claudin 1 and 4 (*Takei* et al., 2015), indicating that a similar AhR-mediated effect could occur in the BBB. One of the most abundant gap junction proteins in the BBB is connexin 43. Connexin 43 expression and gap junction integrity has been shown to be down-regulated by AhR activation (*Andrysik* et al., 2013; *Kabatkova* et al., 2014). The deletion of connexin 43 is known to weaken the BBB, allowing it to open under increased vascular hydrostatic pressure or shear stress (*Ezan* et al., 2012). A recent report suggested that connexin 43 is integral to brain immune quiescence (*Boulay* et al., 2015) and, irrespective of BBB integrity, the deletion of connexin 43 was associated with increased immune cell recruitment across the BBB. Moreover, deletion of connexin 43 leads to activation of the endothelium and chemoattraction, thereby linking a key molecule in the maintenance of BBB integrity with the neuroinflammatory response (*Boulay* et al., 2015).

THE HOLOBIONT AND FURTHER DIRECTIONS

As mounting evidence supports the holobiont model of the host and its microbiome, one of the most important questions facing researchers are the mechanisms by which the microbiota communicates with the host. In humans, we have about 26,600 protein-encoding transcripts which are far fewer in number than that of the rice genome – approximately 46,000 functional transcripts. It is estimated that one thousand different strains of bacteria are expected to contribute up to $4x10^6$ potential mRNAs to the human transcriptome, thus making the human host-plus-microbiome genetic complexity closer to 4,026,600 mRNA transcripts. Thus, considering the holobiont concept, the complexity in humans outnumbers that of rice and other species. If we also bring in all the microRNAs etc., then the complexity of the human physiological road map becomes almost incomprehensible to take in. In conclusion, we have used the microbiome-AhR communication axis to illustrate a small glimpse of the considerable dynamics of microbiome host interactions. The AhR is an evolutionarily conserved ligand induced receptor involved in host-environment interactions. Despite its well-known responsiveness to man-made compounds, such as TCDD, the AhR does not elicit a response to dioxin in invertebrates. Therefore, AhR must execute other evolutionarily important roles in development and homeostasis and studies addressing this signalling pathway holds great promise for future understanding of the holobiont.

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