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Studies of xenobiotic-induced gut microbiota dysbiosis: from correlation to mechanisms

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ABSTRACT

Environmental chemicals can alter gut microbial community composition, known as dysbiosis. However, the gut microbiota is a highly dynamic system and its functions are still largely under-explored. Likewise, it is unclear whether xenobiotic exposure affects host health through impairing host–microbiota interactions. Answers to this question not only can lead to a more precise under-standing of the toxic effects of xenobiotics but also can provide new targets for the development of new therapeutic strategies. Here, we aim to identify the major challenges in the field of microbiota-exposure research and highlight the need to exam the health effects of xenobiotic-induced gut microbiota dysbiosis in host bodies. Although the changes of gut microbiota frequently co-occur with the xenobiotic exposure, the causal relationship of xenobiotic-induced microbiota dysbiosis and diseases is rarely established. The high dynamics of the gut microbiota and the complex interactions among exposure, microbiota, and host, are the major challenges to decipher the specific health effects of microbiota dysbiosis. The next stage of study needs to combine various technologies to precisely assess the xenobiotic-induced gut microbiota perturbation and the subsequent health effects in host bodies. The exposure, gut microbiota dysbiosis, and disease outcomes have to be causally linked. Many microbiota–host interactions are established by pre-vious studies, including signaling metabolites and response pathways in the host, which may use as start points for future research to examine the mechanistic interactions of exposure, gut microbiota, and host health. In conclusion, to precisely understand the toxicity of xenobiotics and develop microbiota-based therapies, the causal and mechanistic links of exposure and microbiota dysbiosis have to be established in the next stage study.

Introduction

Xenobiotics, such as heavy metals, pesticides, anti-biotics, and food additives, can cause adverse effects on human health. The mammalian gut microbiota plays a critical role in food fiber digestion, energy metabolism, immune system development, xeno-biotic biotransformation and so on, and it has been characterized as an "exteriorized organ".[1, 2] Considering the important roles of the gut micro-biota in host health, the effects of xenobiotics on the gut microbiota are extensively explored in the last two decades, and accumulating evidence indicates that many xenobiotics can profoundly perturb the gut microbiota composition to affect host health status.[3] For example, artificial sweeteners can cause glucose intolerance by disturbing the gut microbiota in mice.[4] However, the gut microbiota community is a highly dynamic system, and

numerous factors, such as host genotype, diet, age, and host lifestyles, can significantly alter gut micro-biota composition.[5–7] The inter-individual and intra-individual variation of the gut microbiota is a pervasive phenomenon. Therefore, although exposure of multiple xenobiotics can shift gut microbiota, the changed gut microbiota is not necessary to cause adverse health effects in host bodies. Many studies indicate the association between xenobiotic-perturbed gut microbiota and host diseases, but the causality, for most of the compounds, is still unestablished. To better assess the effects of xenobiotic exposure on the gut micro-biota as well as the subsequent health effects, we need to explore which specific functions of gut microbiota are impaired during exposure. The aims of this review are to summarize the current knowledge of the xenobiotic-driven gut microbiota

dysbiosis, discuss the challenges and principles of future studies, and highlight the demonstrated mechanistic pathways of gut microbiota–host interactions to provide potential future research directions.

Xenobiotic exposure and gut microbiota dysbiosis

Antibiotics

Since the 20th century, antibiotics have been extensively produced and used to treat bacterial infections, which have saved millions of lives. However, many studies reveal that antibiotics increasingly accumulate in natural environments, including soil and aquatic environments.[8–10] With the important roles of the gut microbiota in host health being continuously recognized, the profound and persistent impacts of antibiotic treatment on human gut microbiota have been given special attention.[11,12] Various antibiotics can cause gut microbiota perturbation, including vancomycin, ampicillin, streptomycin, and metronidazole.[13–16] Vancomycin, for example, can reduce the microbial diversity, decrease the gram-positive bacteria, and cause the compensatory increase of gram-negative bacteria.[13,17] The antibiotic-shifted gut microbiota is associated with multiple diseases. A typical example is that antibiotic treatment affects *Clostridium difficile* colonization and host susceptibility to *C. difficile* infection.[18,19] Clindamycin-induced gut microbiota dysbiosis is associated with long-lasting susceptibility to *Clostridium difficile* infection.[20] In addition, vancomycin-induced gut microbiota dysbiosis is associated with decreased insulin sensitivity by modifying bile acid metabolism.[13] Another study has found a cocktail of antibiotics perturbed the gut microbiota to disrupt gut redox dynamics.[21] On the other hand, antibiotics also could reduce disease risk by modifying gut microbiota. For example, rifaximin treatment can improve the level of beneficial bacteria, such as Bifidobacteria and Lactobacilli, to reduce disease risk.[22] Depletion of Firmicutes and Bacteroidetes caused by vancomycin and bacitracin ameliorates insulin resistance in mice with diet-induced obesity.[23]

Heavy metals

Heavy metals are environmental pollutants that affect the health of millions of people in the world.[24] Interactions between gut microbiota and heavy metals have been studied since the last century, mainly focusing on the gut bacteria-performed heavy metal biotransformation.[25–27] Recently, the heavy metal-driven gut microbiota dysbiosis is also investigated. For example, inorganic arsenic exposure has been demonstrated to change gut microbiota community structure, functional gene patterns as well as the metabolome profiles.[28–30] Our previous study has demonstrated that chronic arsenic exposure changed community diversity, reduced the relative abundance of Firmicutes, and shifted the carbohydrate metabolic gene patterns in female mice.[29] Moreover, the sex-dependent effects of arsenic exposure on the gut microbiota are observed.[31,32] The effects of lead exposure are also explored, and both acute and chronic lead exposure can cause gut microbiota dysbiosis in animal studies.[33–37] Short-term lead exposure significantly alters the richness and diversity of the gut microbiota, increases the abundance of α-Proteobacteria, and decreases the abundance of Firmicutes in zebrafish.[33] But another study used mouse model reveals that chronic lead exposure-perturbed gut microbiota is characterized by decreased Bacteroidetes and increased Firmicutes.[34] Chronic lead exposure can shift the gut microbiota metabolic profiles to change the abundance of functional metabolites, such as amino acids, bile acids, and tricarboxylic acid (TCA) cycle-associated metabolites.[34,35] Perinatal lead exposure can induce gut microbiota dysbiosis by increasing Firmicutes and decreasing Bacteroidetes.[36] Likewise, cadmium exposure can also perturb normal gut microbiota community compositions.[38,39] Short-term cadmium exposure can inhibit the growth of Bacteroidetes as well as some probiotics, such as *Lactobacillus* and *Bifidobacterium*, and reduce the copy number of short-chain fatty acid (SCFA)-associated genes.[38] Another study demonstrates the abundance of Firmicutes is decreased in cadmium-treated mice.[39] Gut microbiota dysbiosis caused by early-life cadmium exposure is associated with the exposure-induced fat accumulation in male mice.[40]
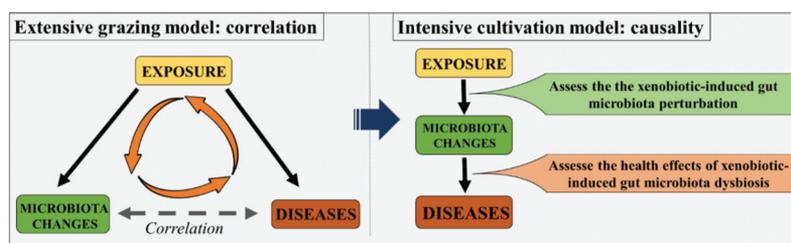
Figure 1. Scheme to show the differences between "extensive grazing model" and "intensive cultivation model".

Pesticides

Pesticide contamination is another serious threat to public health, and the effects of pesticide exposure on the gut microbiota are explored recently. For example, a recent study on honey bees has revealed that glyphosate, one of the most popular herbicides, specifically inhibited the activity of 5-enolpyruvyl-shikimate-3-phosphate synthase enzyme in the shikimate pathway of gut microbiota.[41] This inhibition causes the decline of beneficial gut microbiota with this enzyme and increases the mortality of bees infected with pathogen *Serratia marcescens*. Glyphosate-induced gut microbiota dysbiosis has also been associated with neurobehavioral alterations.[42,43] Organophosphate insecticides are another group of extensively used pesticides, and their effects on the gut microbiota are also investigated. For example, diazinon is found to cause sex-specific effects on mouse gut microbiota, differentially changing the bacterial components, functional gene composition as well as fecal metabolite profiles in male and female mice.[44] Trichlorfon exposure can decrease the abundance of *Lactobacillus* in Japanese quail.[45] Moreover, a recent study revealed that organophosphate-induced hyperglycemia was directly associated with the altered gut microbiome.[46] Organophosphate exposure enriches the xenobiotic biodegrading genes in gut microbiome which promote the gut microbiota to utilize organophosphate to produce acetic acid. The increased acetic acid then enhances the gluconeogenesis in host bodies and finally results in glucose intolerance. Many other pesticides are also found to induce gut microbiota dysbiosis, such as 2,4-D,[47] clorpyrifos,[48,49] imazalil[50–52] and so on. Recent studies of pesticide effects on the gut microbiota is well summarized by a recent review.[53]

Artificial sweeteners

Non-caloric artificial sweeteners are widely used in the food industry to enhance sweet taste without the associated high energy content of caloric sugars. Artificial sweeteners generally have low absorption and metabolism rates, and in a long time, they are considered to be harmless to humans.[54] However, some studies indicate that artificial sweeteners can perturb gut microbiota and cause adverse effects on host health. For example, chronic saccharin consumption can exacerbate glucose intolerance in mice by mediating gut microbiota.[4] Saccharin consumption increases Bacteroidetes phylum, reduced Firmicutes phylum, and also decreases SCFA production. Our previous study has found saccharin-induced gut microbiota shift was associated with liver inflammation.[55] SUCRAM, consisting of saccharin and neohesperidin dihydrochalcone, has been demonstrated to induce the growth of *Lactobacillus*.[56,57] Likewise, sucralose, the most popular artificial sweetener, also can alter gut microbiota. Chronic sucralose consumption causes a shift of a series of gut microbiota genus and enriches the pro-inflammatory genes in mouse gut microbiome.[58] A recent study found that sucralose caused gut microbiota dysbiosis was associated with a high level of hepatic cholesterol and altered bile acid profiles.[59] Some animal studies find that aspartame and acesulfame-K could perturb normal gut microbiota composition,[60,61] and an epidemiologic study also reveals that human gut microbiota diversity is different between aspartame or acesulfame-K consumers and non-consumers.[62] A summary of the effects of artificial sweeteners on the gut microbiota can be found in two recent reviews.[63,64]

Others

The number of compounds that can perturb the gut microbiota is much more than those we listed above. For example, numerous of non-antibiotic drugs have extensive effects on the gut microbiota.[65,66] The interaction of gut microbiota and drugs is tightly associated with the drug side-effects in host bodies. In addition, some environmental pollutants, such as polychlorinated biphenyls (PCBs),[67,68] polycyclic aromatic hydrocarbons (PAHs),[69] and triclosan,[70–72] can disturb the gut microbiota community and affect host health. Our previous studies also demonstrated that nicotine consumption shifted the gut microbiota composition in mice.[73] It can be anticipated that compounds that impact gut microbiota will be continuously reported.

Current difficulties and limitations in xenobiotics–microbiota studies

Previous studies have evaluated the gut microbiota perturbation induced by a series of xenobiotics, but in most cases, we only demonstrated the correlation of xenobiotic exposure, gut microbiota dysbiosis, and disease outcomes, that unexposed and exposed subjects had different gut microbiota profiles. These studies can be regarded as "extensive grazing model" which show the potential effects of those xenobiotics on gut microbiota and provides basic information as well as the theoretical basis for the subsequent research. But to further understand how xenobiotic-induced gut microbiota dysbiosis affects our health and to develop new microbiota-based intervention approaches, "extensive grazing model" has transfer to "intensive cultivation model" in which the causality between xenobiotic-perturbed gut microbiota and host diseases are determined (Figure 1). However, there are many challenges to establish the causal relationship of xenobiotic exposure, gut microbiota dysbiosis, and host diseases.

First, the gut microbiota community is a highly dynamic and complex system, so the specific roles of each type of gut microorganisms in host home-ostasis are unclear. Moreover, many recent studies reveal that the same species from different humans have different characters and can cause very different health impacts on host bodies.[74,75] Therefore,

the exact definition of "healthy/normal gut microbiota" is still undetermined in many aspects, though many studies have conducted to try to define it.[76,77] In addition, notably, although gut microbiota is considered as an extra organ, gut microbiota damage does not necessarily affect our health; after all, they are not a true part of our bodies, which means that xenobiotic-shifted gut microbiota is not always detrimental to host health. It is largely unknown that when gut microbiota shift is bad and can cause adverse health effects on host bodies.

Secondly, functional redundancy is ubiquitous in the gut microbiota community. For example, buty-rate-producing bacteria exist both in the phylum Bacteroidetes and Firmicutes.[78,79] Therefore, community composition changes are not always consistent with functional dysbiosis. But, without knowing the functional perturbation of the gut microbiota, it is hard to evaluate the associated health effects in host bodies. Thus, unless we know the specific function of each bacteria, only investigating the gut microbiota composition changed by xenobiotics wouldn't improve our understanding of the associated health effects.

Thirdly, xenobiotic effects on host bodies and gut microbiota may occur simultaneously. Therefore, although many studies detect gut microbiota shift and host health deterioration during xenobiotic exposure, we actually cannot determine whether the xenobiotic-shifted gut microbiota impairs host health, or the xenobiotic-deteriorated host responses affect the gut microbiota, or this is a dynamic and bi-directional process. Currently, cause and effect have not been demonstrated for most of the studies.

Last but not least, many factors could cause the detectable fluctuation of community composition, including but not limited to diet, bedding caging, sampling time (gut microbiota rhythm), DNA extracting method, and sequencing data analysis. Craigl L. Franklin and other researchers have done some valuable work on the impact of some "peripheral factors" on gut microbiota composition.[80–82] But, in general, the effects of those factors on experiments are rarely quantified and controlled between different studies or even in a single study, which challenges the reproducibility of microbiota-associated studies. Standardization of experimental design remains a critical need in the field.

In summary, to determine the health effects of xenobiotic-induced gut microbiota perturbation, we have to distinguish the natural fluctuation and dysbiosis of the gut microbiota. The former one would not affect host health status, but the gut microbiota dysbiosis has to be linked with adverse health effects in host bodies. To build the links, we need a more refined view to investigate the effects of xenobiotic exposure on the gut microbiota. In other words, we need to explore which specific aspects of gut microbiota are changed by xenobiotics and whether and how these changes affect host health.

Important research principles, strategies, and technologies

Precisely assessing the xenobiotic-induced gut microbiota perturbation

Precisely assessing the xenobiotic-induced gut microbiota perturbation is the prerequisite and foundation of linking gut microbiota dysbiosis with host health conditions and developing microbiota-directed therapies (Figure 1). However, as the high dynamics of the gut microbiota, many factors can influence the gut microbiota composition.

Although controlling the interferences of unrelated variables are required in most of the experiments, for gut microbiota-related studies, it needs to be especially emphasized and concerned, that some "peripheral factors" need to be strictly controlled or normalized, such as diet, drinking water, host genetics, and so on.[80–82] Notably, the cage effects should be highly concerned, because the mice in the same cage frequently share their gut microbiota and tend to have similar gut microbiota profiles.[83] Cage effects decrease the efficiency of individual replicates, and thus multiple cages need to be set in the same experimental group to avoid the false positive or negative results caused by the cage-effects.

In addition, gut microbiota variation in different individuals or groups cannot be completely avoided, which requires us to identify the xenobiotic-caused gut microbiota changes from the neutral fluctuation. How to efficiently filter the true signals from noise is a critical question that needs to be answered. 16S rRNA sequencing, metagenomics, metatranscriptomics, metaproteomics, and metabolomics are powerful technologies that can efficiently identify the changes of gut microbiota,[84,85] but also can induce many false-positive results. Combining multiple technologies can provide a better understanding of the xenobiotic-induced gut microbiota dysbiosis. The *in-vitro* devices, such
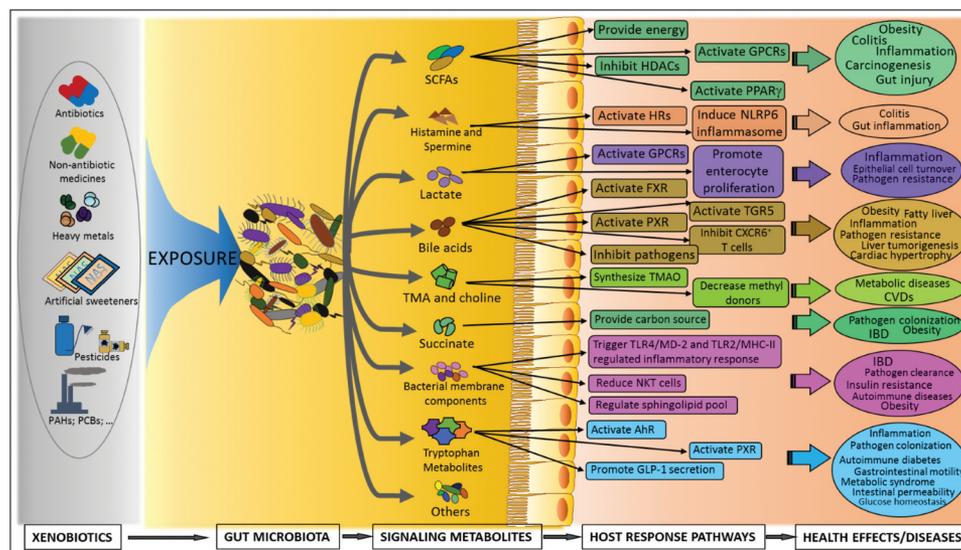

Figure 2. Schematic representation of potential mechanistic links of xenobiotic-induced gut microbiota dysbiosis and adverse health effects. PAHs: polycyclic aromatic hydrocarbons; PCBs: polychlorinated biphenyls; SCFAs: short-chain fatty acids; TMA: trimethylamine; TMAO: trimethylamine-N-oxide; GPCRs: G protein-coupled receptors; HDACs: histone deacetylases; PPARγ: peroxisome proliferator-activated receptor gamma; HR: histamine receptor; IBD: inflammatory bowel disease; TGR5: the G protein-coupled bile acid receptor 1; CVDs: cardiovascular diseases.

as batch-culturing systems, simulators of the human intestinal microbial ecosystem (SHIME), the chemostat-type simulators, and gut-on-chip devices can also help to evaluate the effects of xenobiotics on gut microbiota,[86] although it is still a challenge to exactly mimic the true physiological conditions to maintain the gut microbiota community. In addition, the advance of system biology and computational biology may also provide some other solutions to identify the exposure-induced gut microbiota dysbiosis. For example, recent studies in Dr. Gordon's group successfully utilized the Random Forests, a machine learning approach, to identify the age-discriminatory taxa in children, which allowed to quantitatively assess the unhealthy level of the gut microbiota.[87,88] Another recent study defined the "ecogroup" which used a series of conserved covarying taxa to evaluate the alteration of the gut microbiota under different scenarios.[89] Comparing using the changes of discrete community components, the variation of ecogroup may better reflect the functional changes of the gut microbiota between different groups.

Assessing the health effects of xenobiotic-induced gut microbiota dysbiosis

Comparing with assessing the effects of xenobiotics on the gut microbiota, assessing the specific health effects of xenobiotic-induced gut microbiota dysbiosis are more concerned by toxicologists. Many studies detected the differential gut bacterial profiles in the untreated group and xenobiotic-treated group. However, both the xenobiotics exposure and the exposure-caused gut microbiota dysbiosis can affect host health, and host conditions also can affect gut microbiota. Studies based on traditional exposure study design cannot well determine the causal link of xenobiotic exposure, gut microbiota dysbiosis, and host health impairments.

Germ-free animals and antibiotic-treated animals are powerful tools to explore whether the gut microbiota plays a role in xenobiotic-associated adverse health effects on host bodies. They are analogous to the "gut microbiota knock-out" and "gut microbiota knock-down" animals. By comparing the different responses of conventional-raised animals and germ-free/antibiotic-treated animals, we can determine whether the presence of gut

microbiota can influence the toxic effects of xenobiotics. In addition, gut microbiota transplantation is a key step. By transplanting the xenobiotic-exposed gut microbiota to healthy germ-free or antibiotic-treated animals, we can determine the specific health effects of exposure-driven gut microbiota dysbiosis in host bodies. However, it should be noticed that germ-free animals have largely different physiological conditions with conventional-raised animals, especially of their immune system, and antibiotic treatment may also affect host body conditions. Moreover, transplanting efficiency needs to be carefully evaluated.

Transplanting the exposed gut microbiota to germ-free animals is helpful to evaluate the overall health effects of the whole community, but it still cannot tell us which components are the key factors. After all, not all of xenobiotic-induced changes in gut microbiota will affect host health. Decipher the "black box", that to find the key functional components and pinpoint the key perturbation events, is the critical step to promote the development of microbiota-directed new therapies to treat exposure-caused diseases. However, since our current knowledge about the function of each bacterial components in the gut microbiota is still largely limited, it is still a big challenge to identify the functional taxa, genes, and metabolites. An executable experimental process is first to select those taxa, genes, or metabolites that dramatically changed by exposure as candidates and then validate them by complementary experiments.[90]

Metabolite-driven microbiota–host interactions

Microbiota-derived metabolites play a central role in microbiota–host interactions,[2,91] and previous studies have found various of key metabolites functioning as signaling molecules by which the microbiota affects host homeostasis. Although the whole picture of the microbiota–host interactions is not fully understood, many mechanistic pathways about how microbiota-derived metabolites affect host health have been found by previous studies. Those mechanistic pathways causally link the gut microbiota dysbiosis and host disease outcomes. In the following, we summarize well-demonstrated metabolite-driven microbiota–host interactions, which could serve as the starting points and

measurable indexes to examine the xenobiotic-induced gut microbiota dysbiosis and the associated health effects (Figure 2).

SCFAs

SCFAs, mainly including acetate, butyrate, and propionate, are the end products of anaerobic dietary fiber fermentation. As one group of the most abundant microbiota-synthesized metabolites, SCFAs have been found to play important roles in various physiological processes, especially in energy supplement, immune regulation, gut barrier integrity maintenance, pathogen resistance, and gut-brain axis.

SCFAs function as energy sources to influence host energy homeostasis

Most of SCFAs are absorbed in the intestinal epithelium in ceca and colons. SCFAs, especially butyrate, are the main energy source of colonocytes and provide around 10% of daily caloric in humans estimated by a previous study.[92] The rest SCFAs are mainly metabolized in livers as energy source or used to synthesize host endogenous metabolites. For example, propionate can be utilized in gluconeogenesis to synthesize glucose in livers.[93,94] SCFAs regulated energy homeostasis has been correlated with obesity, and previous studies found that mouse and human subjects with obesity have higher levels of intestinal SCFAs than in lean groups.[95,96]

SCFAs function as G-protein-coupled receptor (GPCRs) ligands to regulate immune response

Activating GPCRs is a critical mechanism of SCFA-conducted immunity regulation.[97,98] GPR43 is a receptor that can be activated by acetate, butyrate, propionate. SCFAs activated GPR43 signaling promotes the proliferation of $CD4^+$ regulatory T (T_{reg}) cells with enhanced Foxp3 and IL-10 levels, which improves colonic homeostasis and protects against colitis.[99] Acetate-activated GPR43 can protect non-obese diabetic mice by increasing the frequency of T_{reg} cells but reducing autoreactive T cells in peripheral tissues.[100] Another study found that SCFA-activated GPR43 promoted the NLRP3 inflammasome activation by stimulating K^+ efflux and hyperpolarization, which provides

health benefits to against colitis.[101] Moreover, previous studies found that SCFA-mediated GPR43 signaling suppressed insulin signaling in adipocytes and also increased the level of TNF-α in anti-inflammatory M2-type macrophages in adipose tissues, that both of them can inhibit fat accumulation.[102,103] GPR41 is another receptor of SCFAs. Propionate-activated GPR41 regulates the generation of macrophages and dendritic cell precursors to protect against allergic inflammation in the lung.[104] In human renal cortical epithelial cells, SCFA-activated GPR41 and GPR43 can reduce TNF-α-induced MCP-1 expression by suppressing p38 and JNK phosphorylation.[105] In addition, butyrate can specifically activate GPR109A. In colonic macrophages and dendritic cells, butyrate-activated GPR109A promotes the differentiation of T_{reg} cells and IL-10-producing T cells, which inhibits colonic inflammation and carcinogenesis.[106] The regulatory role of butyrate on T_{reg} cells by GPR109A can also ameliorate gastrointestinal injury during graft versus host disease.[107] A previous study demonstrated that SCFA-mediated GPR109A and GPR43 activation played a role in food antigens tolerance by increasing mucosal $CD103^+$ dendritic cells.[108]

SCFAs regulate host homeostasis through inhibiting histone deacetylases (HDACs)

Butyrate and propionate can inhibit the HDAC to promote the Foxp3 protein acetylation and then increase the generation of T_{reg} cells.[109] Likewise, butyrate-induced HDAC inhibition can reduce the LPS-stimulated pro-inflammatory mediators in intestinal macrophages, which may protect against ulcerative colitis or Crohn's disease.[110] Another study found that butyrate-regulated HDAC3 inhibition in macrophages reduced the mTOR kinase activity but increased the antimicrobial peptide production, which enhanced the host antimicrobial capability.[111] In the context of graft-versus-host disease, butyrate-promoted HDAC3 inhibition benefits the gut barrier integrity.[112]

Other interactional mechanisms

In addition to the three main mechanistic pathways, SCFAs also can affect host health by some other approaches. For example, butyrate can activate the peroxisome proliferator-activated receptor

γ (PPAR-γ) in colonic epithelial cells to promote the β-oxidation, which limits the aerobic pathogen expansion, such as *Escherichia* and *Salmonella*.[113,114] On the other hand, however, SCFAs can down-regulate the PPAR-γ expression in liver and adipose tissue to inhibit lipid synthesis but increase lipid utilization, which helps to prevent high-fat-diet-induced obesity, reduce hepatic steatosis, and improve insulin sensitivity.[115] A previous study found that propionate could reduce the stability of HilD by disturbing its post-translationally modification and thus repress the *Salmonella* invasion.[116]

Bile acids

Bile acids are originally synthesized from cholesterol in livers known as primary bile acids, stored in gall bladders and then secreted to small intestines to solubilize lipid and fat-soluble vitamins as potent detergents after a meal. Most of the bile acids can be reabsorbed and backed to our bodies, which is called bile acid enterohepatic circulation. Gut bacteria can hydrolyze the amino acid residues (taurine or glycine) in conjugated bile acids to generate free bile acids. Moreover, some gut bacteria also can synthesize secondary bile acids utilizing primary bile acids.[117] Gut bacteria-performed bile acid biotransformation is a critical interaction between the gut microbiota and host, which is not only required to maintain the bile acid homeostasis but also provides key metabolic signaling to multiple tissues in host bodies.[118]

The gut microbiota influences host homeostasis by affecting bile acid-regulated farnesoid X receptor (FXR) signaling

FXR is a transcription factor which presents in multiple tissues and regulates the expression of a wide range of target genes.[119] The most potent endogenous ligands for FXR include chenodeoxycholic acid (CDCA), lithocholic acid (LCA), deoxycholic acid (DCA), and cholic acid (CA), that LCA and DCA are the two secondary bile acids synthesized by gut microbiota.[120] In addition, tauro-β-muricholic acid (TβMCA) has been identified as an antagonist of FXR. Previous studies demonstrated the regulatory roles of gut microbiota on

FXR signaling. Germ-free mice display a higher level of TβMCA and a lower activation level of FXR signaling than conventional mice.[121] Bile salt hydrolase (BSH) activity in gut microbiota, which catalyzes the de-conjugation of conjugated bile acids, is correlated with the TβMCA level as well as the FXR activation.[122] The FXR signal in livers and ilea inhibits bile acid synthesis.[123] Gut microbiota-mediated bile acid metabolism and FXR activation play an important role in the regulation of bile acid pool size.[118] In addition, intestinal FXR signaling is required for gut microbiota-associated lipid accumulation and obesity. Inhibiting intestinal FXR signaling by treating with antibiotics or tempol can reduce high-fat diet-induced hepatic triglyceride accumulation.[124] Modulating gut bacteria to decrease intestinal FXR activation can ameliorate the high-fat diet-induced obesity.[122,125] Moreover, DCA-activated intestinal FXR signaling inhibits prostaglandin E2 production and promotes crypt regeneration, which benefits the colonic wound repair.[126]

The gut microbiota influences host homeostasis by affecting bile acid-regulated TGR5 signaling activation

TGR5 is another transcription factor expressing in a wide range of tissues, which is mainly activated by LCA, DCA, and tauroursodeoxycholic acid (TUDCA), the secondary bile acids synthesized by gut microbiota.[127,128] TUDCA has shown anti-inflammatory effects by activating TGR5 in the nervous system.[128,129] An *in vitro* study reveals that LCA-activated TGR5 can ameliorate cardiac hypertrophy.[130]

Other interactional pathways

There are some other mechanisms of the gut microbiota-regulated bile acid metabolism affecting host health status. The gut microbiota-conducted taurine deconjugation can activate the NOD-like receptor family pyrin domain containing 6 (NLRP6) inflammasome and increase IL-18 level to promote intestinal inflammation [132]. Secondary bile acids, such as LCA and DCA, are known by their high cytotoxicity and carcinogenic effects. DCA has been demonstrated to inhibit tumor-suppressing CXCR6+ natural killer T cells and promote liver

tumorigenesis.[131,132] Hepatic Pregnane X receptor (PXR) can be activated by LCA to prevent LCA-caused liver damage.[133] On the other hand, however, the high toxicity of secondary bile acids also exhibits beneficial effects on host by preventing the colonization of certain pathogens, such as *Clostridium difficile*.[134]

Tryptophan metabolites

Tryptophan is an essential aromatic amino acid which is required for protein synthesis and some key metabolite biosynthesis in mammals. In the last decade, gut microbiota-derived tryptophan metabolism has been extensively studied and it reveals that tryptophan and associated metabolic products play an important role in microbiota–host interactions.

Indole derivatives from tryptophan activate the aryl hydrocarbon receptor (AHR)

Gut microbiota can metabolize tryptophan to multiple indole-containing metabolites, such as indole-3-acetic acid (IAA), indole-3-lactic acid (ILA), and indole-3-propionic acid (IPA), which are important AHR agonists.[135,136] For example, *Lactobacillus reuteri* produced ILA can down-regulate transcription factor Thpok to promote the differentiation of CD4$^+$ T cells into CD4$^+$CD8αα$^+$ double-positive intraepithelial lymphocytes by activating AHR, which benefits to intestinal inflammation.[137] Indole-3-aldehyde (IAld) from *Lactobacillus reuteri* can activate AHR, which promotes IL-22 production to inhibit mucosal inflammation and resistant fungus *Candida albicans* colonization.[138] IAld-induced AHR activation also promotes IL-22 secretion in pancreatic innate lymphoid cells to protect against autoimmune diabetes.[139] Likewise, IAA-induced AHR activation can attenuate inflammatory responses in macrophages and hepatocytes.[138] Moreover, bacteria-derived indoxyl-3-sulfate, IPA and IAld also can limit central nervous system (CNS) inflammation by activating AHR in astrocytes.[140] A previous study revealed that decreased indole derivatives from tryptophan caused a low AHR activation level which was associated with metabolic syndrome, and rescuing AHR activation could significantly improve metabolic dysbiosis.[141]

Other mechanic pathways that indole derivatives performed microbiota–host interactions

In addition to AHR activation, tryptophan-sourced indole derivatives also can modulate host homeostasis by other pathways. For example, IPA can activate PXR to promote the gene expression of tight junctional protein and downregulate enterocyte TNF-α, which decreases intestinal permeability and inflammation.[142] Another study finds that acute treatment with indole promotes the secretion of glucagon-like peptide-1 (GLP-1) in colonic L cells by modulating the voltage-gated K$^+$ channel- and Ca$^+$-dependent action potentials, but continuous exposure to indole reduced GLP-1 secretion by blocking NADH dehydrogenase to decrease ATP synthesis.[143]

Tryptophan-derived neurotransmitters

Gut microbiota also can metabolize tryptophan to different neurotransmitters, such as tryptamine and serotonin.[144,145] Tryptamine is a product of tryptophan catabolism functioning as a β-arylamine neurotransmitter. *Clostridium sporogenes*-produced tryptamine by decarboxylating tryptophan induces ion secretion in intestinal epithelial cells which could affect gastrointestinal motility.[145] Likewise, another study demonstrated that tryptamine could activate GPCR serotonin receptor-4 to promote fluid secretion and accelerate gut transit.[146] Serotonin is another key neurotransmitter in the gut-brain-axis.[144] A previous study demonstrated that indigenous spore-forming bacteria in gut microbiota promoted serotonin biosynthesis in colonic enterochromaffin cells, which increased the gastrointestinal motility and enhanced platelet activation and aggregation.[147] The gut microbiota-regulated peripheral serotonin synthesis plays a mediatory role in host glucose homeostasis.[148] However, how microbiota-derived serotonin affecting neuron system is still largely unclear.

Membrane components of gut microbiota

Multiple gut microbial membrane components can deeply influence host metabolism, especially

regulating host immune response. Lipopo lysaccharides (LPS), a cell wall component of gram-negative bacteria, is possibly the most investigated potent activator of innate immune signaling, and LPS plays an important role in gut microbiota-derived inflammatory responses. The TLR4/MD-2 complex at the cell surface and endosomes is the receptor of LPS, which can be activated by LPS and trigger the downstream immune responses, such as inducing MAP kinases and NF-κB and activating p38 and JNK.[149,150] LPS-induced host inflammation is associated with various diseases, such as IBD inflammatory bowel diseases (IBD), obesity, insulin resistance, and autoimmune and allergic diseases.[151–153]

In addition, capsular polysaccharide A is deeply involved in the *Bacteroides fragilis*-modulated immune responses. Polysaccharide A can bind with MHC-II and the TLR2 receptor in plasmacytoid dendritic cells and then stimulate CD4$^+$ T$_{reg}$ cells to secrete anti-inflammatory cytokine IL-10, which helps to protect against colitis.[154] A previous study found that polysaccharide A stimulated the suppressive CD4(+)CD45RB(low) effector/memory T cells by forming polysaccharide A-MHCII complex, which induced anti-inflammatory responses.[155] Sphingolipids are another group of bacterial membrane components that play a role in the functional interaction between gut microbiota and host metabolism. For example, membrane glycosphingolipids from some *Sphingomonas spp.* can activate natural killer T (NKT) cells and promote the cytokine release which is a benefit to the pathogen clearance during infection.[156,157] In contrast, α-galactosylceramide from *B. fragilis* can reduce colonic invariant NKT (iNKT) cells which attenuates pro-inflammatory responses and protect against colitis.[158] A recent study reveals that *Bacteroides*-derived sphingolipids regulate the pool of host sphingolipids and is correlated with IBD.[159]

Histamine

Histamine can be synthesized by host cells as well as various histamine-secreting bacteria and four different receptors can be activated by histamine, including H1R, H2R, H3R, and H4R.[160] Histamine produced by the gut microbiota has immunomodulatory activity. For example, in human monocytoid cells, *Lactobacillus reuteri*-produced histamine can activate

histamine H2 receptor (H2R) to elevate cAMP levels and inhibit the downstream MEK/ERK MAPK signaling, which inhibits the TLR-induced TNF-α production.[161] Histamine-induced H2R activation plays a critical role in *Lactobacillus reuteri*-driven suppression of intestinal inflammation.[162] Another study found microbiota-associated histamine as well as spermine reduced NLRP6 inflammasome assembly and decreased IL-18 secretion to regulate the host immune homeostasis and affect the host susceptibility to colitis.[163]

Lactate

Lactate is a ubiquitous metabolite in the gut that can be synthesized by some gut bacteria, especially by *Lactobacillus* species. Microbiota-derived lactate accelerates colon epithelial cell turnover in starvation-refed mice by promoting the enterocyte hyperproliferation.[101] Lactate also has immunomodulatory activity that can inhibit NF-κB activation[164] and regulate the TLR signal in intestines.[165] Moreover, lactate can specifically activate GPR81,[166] which can reduce TLR4-dependent inflammation.[167] A recent study found lactate produced by *Bifidobacterium* and *Lactobacillus spp.* promoted the intestinal stem-cell proliferation in a GPR81-dependent manner.[168] In addition, another study indicated that bacteria-derived lactate and pyruvate induced dendrite protrusion in CX3CR1$^+$ cells by activating GPR31, which enhanced the host resistance to intestinal *Salmonella* infection.[169] Lactate can be utilized to synthesize butyrate in gut microbiota, which may also affect host homeostasis.[170]

Trimethylamine (TMA) and choline

Choline, phosphatidylcholine, and L-carnitine can be metabolized to trimethylamine (TMA) by choline TMA-lyase in some gut microbes, which can be further oxidized to trimethylamine-N-oxide (TMAO) by host hepatic flavin monooxygenase.[171] TMAO is known as its proatherogenic effect that enhances atherosclerosis and increases the risk of cardiovascular

diseases.[171,172] Microbiota-derived TMAO can enhance stimulus-dependent platelet activation by promoting Ca^+ release which potentiates thrombosis potential.[173] High serum levels of TMAO are also positively associated with impaired renal function, liver steatosis and diabetes.[174–176] In addition, bacteria-conducted choline metabolism can modulate host homeostasis by affecting host epigenetic programming, that choline consumption by the gut microbiota decreases the availability of methyl-donor metabolites in host bodies resulting in the alteration of global DNA methylation patterns to increase anxiety as well as the susceptibility to metabolic disease.[177]

Succinate

Succinate is a common metabolite participating in the TCA cycle and it can also function as a signaling molecule to mediate microbiota–host interactions, especially by affecting pathogen infection. For example, the *Salmonella enterica* serovar Typhimurium, another enteric bacterial pathogen, can get a competitive growth advantage by utilizing succinate as carbon source.[178] Disturbing normal gut microbiota community by antibiotic and polyethylene glycol treatment increases the succinate level in intestines, which can be utilized as an energy source by *Clostridium difficile* and finally promote the pathogen colonization.[19] In addition, *Bacteroides thetaiotaomicron*-produced succinate can promote the virulence gene expression in another pathogen Enterohemorrhagic *Escherichia coli* by activating the transcriptional regulator *Cra*.[179] Succinate accumulation has also been associated with IBD and obesity.[180–183]

Others

Extracellular ATP in the small intestinal lumen is another metabolic signal performing the interactions between gut microbiota and host. Microbiota-derived ATP is sensed by the ATP-gated ionotropic P2X7 receptor to limit the secretory IgA response in the small intestine by reducing Tfh cell activity, which is important to maintain the mucosal ecosystem homeostasis.[184] Taurine can enhance the NLRP6 inflammasome-induced IL-18 secretion,

which influences the host immune homeostasis and affected the host susceptibility to colitis.[163] Ascorbate, a microbiota-derived metabolite associated with Crohn's disease, can selectively inhibit activated human $CD4^+$ effector T cells by suppressing their energy metabolism and inducing apoptosis.[185]

Conclusions

In conclusion, the effects of xenobiotics on the gut microbiota are extensive and profound. However, our understanding of how those effects contribute to xenobiotic-induced toxic effects in the host is still very limited. The key needs are to precisely assess the xenobiotic-induced functional changes in gut microbiota and decipher which specific functional interactions/pathways between microbiota and host are altered by xenobiotics, which allow the following health effect evaluation. Currently, many mechanistic pathways of gut microbiota–host interactions have been found by previous studies, and more are expected to be discovered in the coming years. Linking those mechanistic pathways with xenobiotic exposure not only can elucidate the specific effects of xenobiotics on gut microbiota and help us better evaluate the toxicity and health effects of xenobiotics, but also can provide valuable targets for the development of microbiota-based new intervention approaches and therapies.

Competing interests

The authors declare that they have no competing interests.

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