HHS Public Access

Author manuscript

Curr Pharmacol Rep. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Curr Pharmacol Rep. 2017 June ; 3(3): 101–113. doi:10.1007/s40495-017-0087-0.

Remote Sensing between Liver and Intestine: Importance of Microbial Metabolites

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Abstract

Recent technological advancements including metagenomics sequencing and metabolomics have allowed the discovery of critical functions of gut microbiota in obesity, malnutrition, neurological disorders, asthma, and xenobiotic metabolism. Classification of the human gut microbiome into distinct “enterotypes” has been proposed to serve as a new paradigm for understanding the interplay between microbial variation and human disease phenotypes, as many organs are affected by gut microbiota modifications during the pathogenesis of diseases. Gut microbiota remotely interacts with liver and other metabolic organs of the host through various microbial metabolites that are absorbed into the systemic circulation.

Purpose of review—The present review summarizes recent literature regarding the importance of gut microbiota in modulating the physiological and pathological responses of various host organs, and describes the functions of the known microbial metabolites that are involved in this remote sensing process, with a primary focus on the gut microbiota-liver axis.

Recent findings—Under physiological conditions, gut microbiota modulates the hepatic transcriptome, proteome, and metabolome, most notably down-regulating cytochrome P450 3a mediated xenobiotic metabolism. Gut microbiome also modulates the rhythmicity in liver gene expression, likely through microbial metabolites, such as butyrate and propionate that serve as epigenetic modifiers. Additionally, the production of host hormones such as primary bile acids and glucagon like peptide 1 is altered by gut microbiota to modify intermediary metabolism of the host.

Summary—Dysregulation of gut microbiota is implicated in various liver diseases such as alcoholic liver disease, non-alcoholic steatohepatitis, liver cirrhosis, cholangitis, and liver cancer. Gut microbiota modifiers such as probiotics and prebiotics are increasingly recognized as novel therapeutic modalities for liver and other types of human diseases.

Keywords

Microbial metabolites; Intestine microbiome; Liver diseases; Bile acids; Short-chain fatty acids; Choline metabolites

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Conflict of interest

The authors of this manuscript declare no conflict of interest.

I. History of research on gut microbiota

Evidence of remote-sensing between gut microbiota and other metabolic organs can be dated back to the early 20th century. It was proposed that exophthalmic goiter is a result of excessive absorption of tryptophan from the intestine due to lack of the indole-producing bacteria, leading to increased levels of the tryptophan derivative thyroxin (1). This highlights the importance of gut microbiota in the normal physiology of thyroid gland. A study in the 1970s demonstrated that the small intestinal transit is slower in diabetic patients with autonomic neuropathy, leading to overgrowth of intestinal bacteria and diarrhea (2). Knowledge on the gut microbiota and its multi-organ interactions has increased exponentially in the 21st century as a result of technical advancements in metagenomics and metabolomics. The Human Microbiome Project, funded as an initiative of the National Institute of Health (NIH) Roadmap for Biomedical Research, has utilized high-throughput sequencing technologies to systematically characterize the human microbiome, providing a first draft of the reference metagenomic landscape in healthy situations (3). The biological functions of various microbial metabolites, such as secondary bile acids, acetate, indole, propionate, butyrate, and methane, have been characterized through advanced metabolomics techniques. In addition, gut microbiome modifiers have long been used to treat human diseases. Antibiotics are used to eliminate harmful bacteria in various infectious diseases, whereas probiotics have served as an effective, new therapeutic modality for many human diseases related to both GI and other organs. Early life disruption of gut microbiome by C-section, antibiotics, probiotics, dietary supplement, hygiene, and pets has been linked to a wide spectrum of delayed onset of human diseases (4).

The impact of gut microbiome as a collective community on human health has been recognized in intermediary metabolism using a metagenomic approach and germ-free (GF) mice. Comparisons of gut microbiota between obese and lean mice, as well as between obese and lean human subjects using 16S rRNA sequencing and biochemical approaches have demonstrated that an “obese microbiota” configuration, evidenced by increased Firmicutes/Bacteroidetes ratio, has an increased capacity to harvest energy from the diet (5). Studies on the core gut microbiome in obese and lean twins have shown that obesity is associated with phylum-level changes in the gut microbiota, reduced bacterial diversity and other associated metabolic phenotypes (6). Intestinal bacteria such as *Prevotella copri* and *Bacteroides vulgatus* produce branched chain amino acids, which are increased in serum of insulin-resistant individuals, whereas in mice *P. copri* induces insulin resistance, aggravates glucose intolerance and augments circulating levels of branched-chain amino acids, suggesting that gut microbiome is a target for metabolic disorders (7). In addition to obesity, gut microbiota is at least partially responsible for growth impairment in malnourished children, suggesting a great potential to employ probiotic supplement to treat under-nutrition (8).

II. Gut microbiota and liver physiology

II-1. Gut microbiota and the hepatic transcriptome, proteome, and enzyme activities

Gut microbiota profoundly influences the hepatic expression of genes important for xenobiotic biotransformation and intermediary metabolism. A microarray study has

identified a cluster of 112 differentially regulated genes between livers of convention (CV) and GF mice, most of which are involved in xenobiotic metabolism (9). Another recent study has utilized quantitative proteomic analysis to demonstrate that 825 and 357 liver and kidney proteins respectively are differentially expressed in GF mice compared to CV mice, whereas a total of 306 and 178 proteins are differentially regulated in liver and kidney of antibiotics-treated mice, respectively, as compared to vehicle-treated CV mice. These proteins include drug-metabolizing enzymes and transporters as well as mitochondrial proteins (10). In summary, dysbiosis in the gut markedly alters the expression and activities of distinct hepatic genes, highlighting the importance of the gut-bacteria-liver axis for drug metabolism and energy metabolism pathways.

II-2. Gut microbiota and xenobiotic metabolism

A growing body of literature has demonstrated that gut microbiota is a novel regulator of xenobiotic metabolism (11–15). There are two ways that gut microbiota contributes to this process: 1) gut microbiota can directly utilize distinct microbial enzymes to metabolize drugs and other xenobiotics to form active or inactive metabolites; 2) gut microbiota can indirectly modify the host xenobiotic metabolism by generating certain microbial metabolites, which can enter the enterohepatic circulation and reach the liver and other organs at sufficient concentrations to modulate host receptors (14).

Examples for the direct effect of gut microbiota on xenobiotic metabolism include *Eggerthella lenta*-mediated inactivation of the cardiac glycoside digoxin using cardiac glycoside reductase, which is profoundly influenced by protein (especially arginine) intake (16, 17). Another example is the microbial β-glucuronidase mediated reactivation of the glucuronide metabolite of the anticancer drug irenotecan, and chemical inhibitors targeting microbial β-glucuronidase has been shown to be promising in the alleviation of irenotecan toxicity in mice (18). Gut microbiota has also been shown to alter the efficacy and/or toxicity of many other xenobiotics, such as the cholesterol-lowing drug simvastatin, the anti-Parkinson drug L-dopa, the antibiotic and anti-inflammatory drug sulfasalazine, anticonvulsant pentobarbital, and the pain reliever acetaminophen, as was reviewed by Navk and Turnbaugh (12), and Klaassen and Cui (15). Gut microbiome has also been shown to be a major player in the toxicity of environmental pollutants through five core enzyme families (azoreductases, nitroreductases, β-glucuronidases, sulfatases, and β-lyases); conversely, various environmental contaminants can alter the composition and/or the functionality of intestinal bacteria [168].

In addition to direct microbial metabolism, indirect microbial metabolism through the interactions between microbial metabolites and host receptors in liver and other organs is increasingly recognized. Along these lines, a meta-pharmaco-genomic approach has been recently proposed to stratify patients for precision medicine (14). One classic example indirect effect of gut microbiota on host xenobiotic metabolism is the regulation of the major phase-I oxidation enzyme Cytochrome P450 3a11 (Cyp3a11). CV mice treated with the antibiotics such as ciprofloxacin, ampicillin, levofloxacin, or vancomycin-imipenem combination, have reduced hepatic expression and enzyme activity of Cyp3a11, and this correlates with decreased lithocholic-acid (LCA)-producing bacteria in feces and taurine-

conjugated LCA in liver, whereas LCA-replacement in GF mice raised the Cyp3a11 expression in liver (19, 20). Using RNA-Seq, RT-qPCR, enzyme activity assays, chromatin immunoprecipitation, and targeted proteomics, we have demonstrated that many important drug metabolizing enzymes and transporters are differentially regulated by gut microbiota during liver development and in adult ages such as lack of gut microbiota, probiotic (VSL3) supplementation, and conventionalization procedures. Specifically, we have shown that reduced pregnane X receptor (PXR) signaling and increased peroxisome proliferator-activated receptor α (PPARα) signaling may at least in part contribute to decreased expression of Cyp3a but increased expression Cyp4a gene clusters, respectively (21–23).

II-3. Gut microbiota and the hepatic diurnal rhythm

The mammalian circadian clock regulates various behavioral and metabolic processes. The core circadian components include the heterodimer formed by Clock and Bmal1, which initiates the transcription of many circadian oscillators in the primary feedback loop, including Per1, 2, and 3, as well as Cry1 and 2. The Per-Cry complex translocates back to the nucleus to repress their own transcription by inhibiting the Clock:Bmal1 function. The central clock is located in the suprachiasmatic nucleus (SCN), whereas peripheral clocks are ubiquitously expressed. The peripheral clocks are cell-autonomous and can function independently of the central clock. In liver, which is the major organ for drug metabolism and nutrient homeostasis, approximately 10% of the transcriptome is rhythmically expressed, including many genes involved in the metabolism of glucose, lipids, and bile acids, and this correlates with day-night variations in Clock-DNA binding sites (24). Interestingly, the gut microbiome also displays a circadian rhythm pattern in both composition and function, which is regulated by the host circadian clock, gender, and feeding behavior (25). Reciprocally, gut microbiome is a novel key regulator in maintaining host hepatic circadian rhythm, in that GF mice exhibit markedly impaired hepatic circadian clock gene expression, and specific bacterial metabolites (such as short chain fatty acids) in CV mice directly modulate circadian clock gene expression in hepatocytes (26). Antibiotics-induced microbial depletion leads to a loss in the rhythmicity in the hepatic expression of oxidative phosphorylation-related genes, whereas non-oscillating genes such as those involved in amino acid and fatty acid metabolism gain rhythmicity in liver. Mechanistically, disruption of the rhythmicity in gut microbiota reprograms the epigenome and transcriptome in colon and liver likely through microbiota-derived metabolites such as lipids, amino acids, carbohydrates, vitamins, nucleotides, and xenobiotics. Specifically, it has been speculated that butyrate, which is a short-chain fatty acid produced by bacterial fermentation of fiber in colon, as well as propionate, which are histone deacetylase inhibitors, may circulate via the hepatic portal vein to epigenetically regulate the oscillating chromatin modifications (27).

III. Gut bacterial metabolites, co-metabolites, and other microbial constituents as multi-organ sensors

The gut microbiota has the capacity to produce a diverse range of compounds that play a major role in regulating the activity of distal organs. Gut microbial metabolites, co-metabolites, and other microbial constituents (28), such as secondary bile acids, short chain fatty acids, choline metabolites, indole-derivatives, ethanol, and endotoxins, have many

biological functions, as summarized in Table 1. In addition to the *in situ* function in the GI tract, these bacterial metabolites can act on various extra-intestinal organs through portal blood and systemic circulation and thus modulate host metabolism and health in a broader manner, which will be discussed in detail.

III-1. Bile acids (BAs)

As the endogenous metabolic end-product of cholesterol in liver, BAs have recently been shown to be important signaling molecules and metabolic regulators that control glucose and lipid homeostasis as well as energy consumption (29). The majority of BAs that are secreted into the intestinal lumen are reabsorbed from the terminal end of the small intestine and return to the liver through the portal blood. This enterohepatic circulation of BAs is facilitated by multiple transporters in both liver and intestine (30, 31). The BAs that are synthesized from cholesterol and conjugated with taurine or glycine on the side chain or sulfate on the steroid nucleus in the liver are called primary BAs, which further undergo deconjugation, dehydroxylation, epimerization, and oxidation into secondary BAs by intestinal bacteria, primarily in the lumen of large intestine. Cholic acid (CA) and chenodeoxycholic acid (CDCA) (and muricholic acids in mice), are primary BAs. Some secondary BAs include deoxycholic acid (DCA), LCA, and ursodeoxycholic acid (UDCA) (32).

BAs are closely involved in a multitude of physiological and pathological processes, through interactions with two major BA receptors, namely the nuclear receptor farnesoid X receptor (FXR/Nr1h4) and the membrane-bound G-protein coupled receptor TGR5 (GPBAR1). We have several publication demonstrating that BA homeostasis can be affected by various factors, such as age (30, 33), gender (30), diet (34, 35), and drugs (32). Disruption of the enterohepatic circulation of BAs can give rise to cholestasis and NAFLD, which may progress to fibrosis and cirrhosis. FXR has been known to exert tissue-specific effects in regulating BA synthesis and transport (31). Reduced intestinal availability of BAs reduces stimulation of FXR. This may induce hepatic BA overload and associated hepatotoxicity through reduced action of intestinal fibroblast growth factor 19 (FGF19 in human or FGF15 in mice). Maintaining the enterohepatic circulation of BAs prevents hepatic cholestasis through a FXR feedback pathway. Changes in gut microbiota composition may induce liver disease (36).

Bacteria are closely involved in the synthesis and enterohepatic circulation of BAs, which regulate the hepatic expression of genes responsible for crucial metabolic and inflammatory pathways involved in many liver diseases. This is an important mechanism through which the intestinal microbiota interact with the host and determine the healthy/disease states of various organs of the host. Perturbation of intestinal bacteria affects the ratio of conjugated and unconjugated BAs and the ratio of primary and secondary BA, which have differential effects on BA receptors. As expected, an altered BA profile has been observed in gnotobiotic animals (37, 38).

At the same time, the bacteriostatic effects of BAs can also directly act as detergents on bacterial membranes and alter intestinal microbiome as detergents (39). BAs can also inhibit bacterial proliferation indirectly by modulating host gene expression, for example,

increasing production of antimicrobial proteins angiogenin 1 and RNase family member 4 in intestine. Moreover, FXR activation is required to maintain the integrity of intestinal barrier, whose disruption will cause bacterial translocation and immune activation that ultimately alters microbiota composition (40). In short, the interaction between intestinal bacteria and BAs are bidirectional.

BA homeostasis and composition are closely related to the development of various diseases. Several BAs have been shown to ameliorate NAFLD, such as CA (41), UDCA (42), and taurine-conjugated UDCA has been effective to improve NASH (43, 44). Alteration of serum BAs is associated with NASH (45) and ALD (46) in animal models. A BA-derivative 6-ethylchenodeoxycholic acid called obeticholic acid is a potent FXR activator that reduces liver fat in animal models of fatty liver disease (47). The obeticholic acid has been shown to attenuate liver inflammation and fibrosis in patients with type 2 diabetes mellitus and NAFLD in a phase 2 clinical trial (48). Activation of BA nuclear receptor FXR decreases triglyceride content in liver by decreasing de novo lipogenesis and increasing fatty acid beta-oxidation (49). Recent investigations demonstrate that FXR also plays a principle role in regulating lipid metabolism and suppressing inflammation in the liver (40). Activation of BA membrane receptor TGR5 in brown adipose tissue and muscle increases energy expenditure and attenuates diet-induced obesity in mice. The TGR5 agonist INT-777 caused release of intestinal GLP-1, and reduced adiposity and hepatic steatosis in mice placed on high-fat diets (50). Furthermore, FXR activation decreases liver inflammation by inhibiting NF-kB signaling and activation of another BA receptor TGR5 decreases cytokine expression in Kupffer cells (49). Patients with cirrhosis have decreased fecal BAs and a reduced ratio of secondary versus primary BAs (51). The bacterial BA metabolite UDCA abrogates senescence in vitro on cholangiocytes from a PSC animal model (52).

Another bacterial metabolite DCA provokes the senescence-associated secretory phenotype in hepatic stellate cells, which secretes inflammatory factors and mitogens and ultimately promotes HCC development in animals with neonatal exposure to a chemical carcinogen followed by a high-fat diet. Notably, blocking DCA production or reducing gut bacteria efficiently prevents HCC development in obese mice (53). This suggest a crucial role of the obesity-induced microbial metabolite in promoting HCC (54). When BA homeostasis is disrupted by FXR deficiency, the resulting inflammation and injury ultimately causes uncontrolled cell proliferation and tumorigenesis in the liver (55). Despite the close relationship observed between BA composition and the development of various diseases, whether intestinal microbiota contributes to the BA changes in these diseases in not conclusive.

III-2. Short-chain fatty acids (SCFAs)

Another group of important gut bacterial metabolites are SCFAs, predominantly butyrate, acetate and propionate. SCFAs, which are the major products of the bacterial fermentation of carbohydrates and proteins in the gut, represent the signature hormones of the microbiota and may mediate many of the functions assigned to the microbiota through classical endocrine signaling (56).

SCFAs, particularly butyrate, are a significant source of energy for gut enterocytes, and support the gastrointestinal barrier function through the stimulation of tight junction and mucous production. Alterations in the intestinal microbiota impact the energy extraction and fermentation of dietary fibers into oligosaccharides, monosaccharides, and SCFAs (57). Some SCFAs (such as lactic acid, propionic acid, or butyric acid), which are fermentation products of *Lactobacilli*, are important to intestinal epithelial integrity and help *Lactobacilli* adhere to intestinal cells, protecting against pathogens (58). Butyrate is important for colonic integrity, as it acts as a significant energy source for colonocytes (59). The major bacterial sources of butyrate are *Clostridia, Eubacteria, Roseburia* (60). By preserving the gut barrier, butyrate prevents bacterial translocation to the circulation.

Several in vitro studies have suggested the possible functions of SCFAs in other organs as well as the intestine. For example, they can pass the blood-brain barrier via monocarboxylate transporters, and thereby enter the central nervous system (CNS) (61), providing a plausible mechanism through which they can enter the CNS. SCFAs are also proposed to increase satiety following the consumption of a diet rich in fiber, because they can activate free fatty acid receptors 2 and 3 (FFAR2/3; GPR43/41) to trigger production and release of GLP-1, peptide YY (PYY), ghrelin, and leptin (28). However, it remains to be definitively established whether microbiota-derived intestinal SCFAs are at sufficiently high concentrations for their alterations to influence the CNS.

Circulating SCFAs (such as butyrate and propionate) once produced can travel to remote sites. SCFAs are detectable in portal and hepatic venous blood, and liver can use propionate and butyrate for energy metabolism in physiological conditions. The liver of patients with stable cirrhosis is able to use portal-derived butyrate and propionate (62). In liver, propionate inhibits lipogenesis by acting on the transcription of several rate-limiting step enzymes involved in de novo lipogenesis, including acetyl-coenzyme A carboxylase, fatty acid synthase, malic enzyme, and glucose-6-phosphate dehydrogenase (63). Apart from limiting food intake, some of the molecules produced in response to SCFAs (e.g. GLP-1) also ameliorate insulin sensitivity. SCFAs are also involved more directly in glucose regulation through their participation in gluconeogenesis, as propionate is used as a gluconeogenetic substrate (64). A lack of SCFA receptors leads to decreased adiposity (65). In humans, obesity has been associated with an increased concentration of SCFAs in the stool (66). As a consequence, the dietary fibers and their fermentation products such as SCFAs are promising tools to reduce steatosis and inflammation.

SCFAs are also involved in the regulation of inflammatory signals within the liver. SCFAs have also direct anti-inflammatory effects. This is shown in animal models where deficiency of the SCFA receptor GPR43 is associated with an increase in inflammatory tone (67). Specifically, both propionate and butyrate have been shown to attenuate the expression of pro-inflammatory cytokines by leukocytes and adipocytes. SCFAs also induce the expression of anti-inflammatory cytokines, such as IL-10, and may be involved in the synthesis and function of T-regulatory cells (49). SCFAs can reduce inflammation by downregulating inflammatory cytokine production and nuclear factor kappa B activity in human peripheral blood mononuclear cells and co-culture of macrophages and adipocytes

(68). Administration of tributyrin, a prodrug of butyrate and a dairy food component attenuates LPS-induced acute liver injury (61).

III-3. Choline metabolites

Microbial metabolic activities also include the metabolism of choline, important for lipid metabolism, to trimethylamine (TMA) (69). Once synthesized by the intestinal microbiota, TMA can be further metabolized in the liver to trimethylamine-N-oxide (TMAO), which, when present in the circulation at sufficient concentrations, can contribute to the development of cardiovascular disease (70). The conversion of dietary choline by the intestinal microbiota to TMA can result in choline deficiency. Hepatic choline deficiency results in decreased VLDL efflux, producing hepatic steatosis (28, 57). Reducing the bioavailability of choline can contribute to nonalcoholic fatty liver disease and altered glucose metabolism both in mice (71) and humans (70).

III-4. Indole-derivatives and other neuroactive compounds

Gut bacteria metabolize amino acids into specific metabolites including indoles and ammonia. Tryptophan is metabolized by *Clostridium sporogenes* into indole-3-propionic acid (72). Manipulating the microbial composition of the intestinal tract modulates plasma concentrations of tryptophan, an essential amino acid and precursor to serotonin, a key neurotransmitter within both the enteric and central nervous systems. In hepatic encephalopathy (HE), gut microbiota and their metabolites are altered, gut epithelial barrier is impaired and the blood-brain barrier has increased permeability. Inflammatory signals as well as neuroactive microbial metabolites reach the brain where they induce regional inflammation. Among the different mechanisms connecting microbial metabolites and HE, several strong associations have been found between both ammonia and indoles/oxindole levels. Altered brain gut microbiome interactions in HE provide targets for novel treatment approaches, including prebiotics and probiotics, and microbe-specific antibiotics (63).

It was recently shown that indoles, a microbial tryptophan metabolite, appear to be an agonist for aryl hydrocarbon receptor (AhR) (73, 74) and indole-mediated activation of human AhR within the gastrointestinal tract may provide a foundation for inter-kingdom signaling between the enteric microflora and the immune system to promote commensalism within the gut (75). Indoles have also been found to induce some cytochrome P450s through an AhR-mediated mechanism in liver (76). Conversely, AhR influences the community structure of the intestinal microbiota (77).

III-5. Ethanol

NAFLD describes the liver histopathology in non-drinkers that resembles alcoholic liver injury. Recent data suggest that despite the lack of alcohol consumption, there may be a component of ethanol-induced injury in NAFLD (78, 79). Children with NAFLD and NASH not only have dysbiosis (increased *Proteobacteria*) but also increased plasma levels of ethanol compared to lean healthy controls and obese children without NASH (78). The intestinal microbiota-derived ethanol contributes to steatosis by increasing *de novo* lipogenesis (80), decreasing fatty acid β-oxidation (81) and decreasing the hepatic export of triglycerides (82). In addition, ethanol affects intestinal permeability, resulting in bacterial

translocation and ultimately hepatic inflammation (83). NAFLD patients have increased intestinal permeability associated with elevated plasma ethanol and endotoxin levels (79). Treating patients with NASH and small intestinal bacterial overgrowth with antibiotics leads to a decrease in endogenous ethanol synthesis, suggesting that targeting the intestinal microbiota may be an important approach to the management of NAFLD (49).

III-6. Endotoxins

Lipopolysaccharides (LPS) or endotoxin are major component of the outer membrane of Gram-negative bacteria and provoke a strong immune response. Changes in intestinal microbiota composition can lead to increased intestinal permeability, mesenteric inflammation and endotoxemia in animals, which can be reversed by antibiotics or prebiotics (84, 85). In humans, NAFLD has been found to be associated with increased circulating endotoxin levels, suggesting translocation of bacteria and/or their structural components from the gut to the circulation (86). It is noteworthy that the degree of NAFLD is correlated with endotoxemia level, in that NASH patients have higher endotoxin levels than those with simple steatosis (87). Bacterial components are recognized by the innate immune system by Toll-Like Receptors, which are crucial for the development of hepatic steatosis and inflammation in mice (88, 89) and humans (90).

IV. Host hormones that are altered as a result of changes in gut microbiota

Gut microbiota not only generates direct microbial metabolites, which travel through the portal blood to interact with liver and other metabolic organs, but also alters the production of certain host hormones to modulate the signaling pathways of various organs in the host (91). Examples of these host hormones are described in this section (Table 2).

In addition to generating secondary bile acids as direct microbial metabolites, gut microbiota also inhibits bile acid synthesis in the liver by alleviating FXR inhibition in ileum. In mice, a key molecule that is involved in this process is a primary bile acid called tauro-βMCA, which is a naturally occurring FXR antagonist and its level is increased in GF mice (92). T-βMCA levels are increased during the treatment of tempol, which is an anti-obesity drug, suggesting that gut microbiota is important in modulating the host T-βMCA-FXR signaling during obesity (93).

GLP-1 is a 30 amino acid peptide hormone that is produced in the intestinal epithelial endocrine L-cells, and is released in response to food intake to stimulate insulin secretion and inhibit glucagon secretion. Exaggerated secretion of GLP-1 is thought to be responsible for postprandial reactive hypoglycemia, whereas decreased secretion of GLP-1 has been implicated in the development of obesity (94). BAs activate their cell-surface receptor TGR5, which through cAMP-dependent pathways promotes GLP-1 secretion from intestine (95, 96). GF mice have increased plasma levels of GLP-1, coincident with a marked increase in total BAs in serum, liver, bile, and ileum, as well as decreased fecal excretion of BAs (97, 98). These data indicate that the increased GLP-1 production seen in GF mice is caused by enhanced TGR5 signaling (due to increased availability of BAs as its ligand).

Another host hormone that is critically regulated by gut microbiota is the lipoprotein lipase inhibitor fasting-induced adipocyte factor (Fiaf). Gut microbiota suppresses Fiaf in intestinal epithelium and in circulation, thereby promoting deposition of triglycerides in adipocytes (99). In GF mice, increased intestinal and circulating Fiaf levels subsequently up-regulates peroxisome proliferator-activated receptor coactivator 1α (PGC1α); the absence of gut microbiota also up-regulates the muscle AMP-activated protein kinase which increases the levels of carnitine: palmitoyl transferase-1 (CPT-1) (100). Therefore, there is a gut microbiota-muscle-adipose axis to regulate obesity through modulating levels of the Fiaf hormone.

Gut microbiota is also essential in maintaining the constitutive levels of brain-derived neurotrophic factor (BNDF) and the function of N-methyl-D-aspartate receptors (NMDARs) in the central nervous system, via changes in neurotransmitter function by affecting modulatory mechanisms such as the kynurenine pathway or actions of SCFAs in the brain (101).

Gut microbiota promotes an increase in insulin-like growth factor 1 (IGF-1), which is known to promote bone growth (102). Colonization of GF mice with gut microbiota from CV mice increases serum IGF-1, which is produced by liver and adipose tissue (102). In addition, SCFA supplementation also leads to an increase in serum IGF-1 levels (103).

V. Gut microbiota and liver diseases

As the organ in closest contact with the intestinal tract, liver is exposed to a substantial amount of bacterial components and metabolites through portal circulation. Moreover, the liver plays a crucial role in defense against gut-derived materials forming the gut-liver axis. Gut microbiota behaves as a metabolic and immunological organ that can mediate responses within the host to external stimuli. Therefore, it is recommended to complement the concept of the gut-liver axis with the gut-microbiota-liver network because of the complex interplay between microbiota components and metabolic activities (28).

Among the extra-intestinal diseases in which the gut microbiota is thought to play a role in, various liver disorders have recently been found to be closely associated with altered bacterial composition of the gut microbiota (called dysbiosis), such as alcoholic liver diseases, non-alcoholic fatty liver diseases and steatohepatitis, liver cirrhosis, primary sclerosing cholangitis, hepatic viral diseases, and hepatocellular carcinoma (HCC). However, the exact microbial metabolites responsible for the pathogenesis of individual liver diseases generally remain elusive. In this review, we highlight the liver diseases in which gut microbiota may serve as a novel therapeutic target, although further studies are needed to reveal the mechanism of gut microbiota in the progression and treatment of liver diseases.

V-1. Alcoholic liver diseases (ALD)

Preclinical and clinical studies have suggested the important role of gut microbiota in ALD. Impaired intestinal barrier, dysbiosis, and endotoxemia are well-known processes during the development and progression of ALD. Tight junctions are disrupted by acetaldehyde production from ethanol directly and by intestinal inflammatory cell-derived tumor necrosis

factor-α-induced myosin-light chain kinase signaling (63). A leaky gut barrier allows bacterial translocation, which is the escape of gut bacteria and their products through the intestinal mucosa to the outside of the intestine via portal or systemic circulation. This translocation is considered pathogenic in patients with chronic liver diseases who fail to remove bacteria or bacterial products, which leads to the accumulation of pathogen-associated molecular patterns that are recognized by Toll-like receptors in the liver and contribute to host's immune system as well as liver damage and diseases in a chronic setting (104). Chronic alcohol administration leads to bacterial overgrowth along almost the entire gastrointestinal tract as well as dysbiosis characterized by reductions in probiotic bacteria such as *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Lactococcus* (105). Additionally, probiotic *Lactobacillus* has been shown to effectively rescue ALD injury in animals (106) and humans (107). Moreover, intestinal permeability and dysbiosis are associated with alcohol dependence. However, the contribution of the intestinal microbiome to liver disease goes beyond simple translocation of bacterial products that promote hepatic injury and inflammation. Microbial metabolites produced in a dysbiotic intestinal environment and host factors are equally important in the pathogenesis of liver diseases (108). Alcohol, as an initiating liver insult, and its associated microbial products might synergize to promote progression of liver disease. Changes in the intestinal microbiome (particularly bacterial overgrowth) and increased bacterial translocation both contribute to alcoholic liver disease.

V-2. Non-alcoholic fatty liver diseases (NAFLD) and steatohepatitis (NASH)

Obesity and insulin resistance are risk factors for fatty liver disease and are associated with changes in the intestinal microbiome (5). High-fat diets (HFD) result in dysbiosis and intestinal bacterial overgrowth. NAFLD progression can be regulated by inflammasome-mediated dysbiosis. Microbial composition is altered by inflammasomes, characterized by increase in *Prevotella*. In turn, dysbiosis causes the disruption of tight junctions in enterocytes, leading to leaky gut, bacterial translocation, and ultimately liver inflammation.

Despite some controversy, many studies have found increased Bacteroides in NASH patients and increased Firmicutes *lactobacilli* is often associated with liver steatosis in NAFLD patients and animal models (58). Another study found that NASH patients had lower fecal abundance of *Faecalibacterium* and *Anaerosporobacter* but higher abundance of *Parabacteroides* and *Allisonella* (109). Moreover, the use of Lepicol probiotic formula (containing *Lactobacillus plantarum, Lactobacillus deslbrueckii, Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacterium bifidum*) for 6 months decreases liver fat and serum AST level in NASH patients (110). A mixed probiotic-prebiotic treatment (Lepicol probiotic and prebiotic formula) in NASH patients leads to reduction in Firmicutes and increase in Bacteroidetes, which is correlated with improved intrahepatic triglyceride content (109).

V-3. Liver cirrhosis

Most patients with liver cirrhosis have intestinal bacterial overgrowth, demonstrated by quantitative analyses of bacterial cultures from jejunal aspirates (111). In addition to their increased intestinal burden of bacteria, they also exhibit taxonomic differences in microbial communities, compared to people without cirrhosis, but also an increased intestinal burden

of bacteria. A common feature of cirrhosis is an increase of potentially pathogenic bacteria, accompanied by reduced proportions of beneficial bacteria. Serum lipid levels of organic acids have significant correlations with specific fecal flora in liver cirrhosis patients. Specifically, *Lactobacillus* and decosahexaneoic acid are found to be positively correlated, as well as *Candida* and eicosapentaenoic acid or eicosapentaenoic acid/arachidonic acid (68).

Fecal microbial communities are distinct in patients with cirrhosis compared to healthy individuals. The increased prevalence of potentially pathogenic bacteria, such as *Enterobacteriaceae* and *Streptococcaceae*, with the reduction of beneficial populations such as *Lachnospiraceae* may affect prognosis in patients with cirrhosis (112). At the genus level, *Bacteroides* was the dominant phylotype in both groups, but was significantly decreased in the liver cirrhosis group. Of the remaining genera, *Veillonella*, *Streptococcus*, *Clostridium* and *Prevotella* were enriched in the liver cirrhosis group, while *Eubacterium* and *Alistipes* were dominant in the healthy controls (113).

V-4. Hepatic viral diseases

Gut microbiota appears to play a critical role in age-related immune clearance of hepatitis B virus (HBV) (114). It has been indicated that chronic HBV patients with liver cirrhosis have different microbiota compared to healthy people (112, 113). A recent case-controlled, open-label pilot trial has demonstrated the efficacy of fecal microbiota transplantation in HBV e-antigen positive patients, especially in those who could not otherwise cease the oral antiviral treatment even after long-term treatment (115). This suggests a benefit from modifying the gut microbiota for chronic HBV treatment, however, larger trials will be needed to draw a definite conclusion in the future.

V-5. Biliary diseases

The cholangitis animal model have different gut microbiome from healthy animals and raising diseased animals in germ-free condition diminishes bile duct diseases, which suggests that intestinal microbiota contributes to biliary inflammation in this animal model (116). A clinical study reported that gut microbiota profile in primary sclerosing cholangitis (PSC) patients was different from healthy people's, showing a decrease in 11 genera and increase in *Veilonella* genus in patients vs controls (117). A similar finding of increased *Veilonella* in PSC patients was observed in a recent study (118). A recent mucosa-associated microbiota study showed that PSC patients have increased *Barnesiellaceae* at the family level and *Blautia* at the genus level (119). This suggests an important role of intestinal microbiota in PSC.

VI. Gut microbiota and multi-organ interactions

Recently, accumulating evidence in the literature has demonstrated that gut microbiota not only exerts important functions in the gastrointestinal tract such as food digestion and energy harvest, but also plays novel roles in many other critical metabolic organs. Classification of the human gut microbiome into distinct "enterotypes" has been proposed to serve as a new paradigm for understanding the interplay between microbial variation and human disease phenotypes, as many organs are affected by gut microbiota modifications during the

pathogenesis of diseases (120). Although the exact molecular mechanisms for gut microbiota-mediated “remote sensing” in these organs have not been fully understood, it has become increasingly recognized that microbial metabolites that travel from the gut to certain organs may serve as critical players during this process. Whereas the major focus of this review is between gut microbiota and liver, the interplay of gut microbiota and other important extrahepatic organs is briefly summarized in this section.

In brain, exploration of gut microbiota offers new insights into further understanding neurodevelopment and behavioral phenotypes such as inter-individual variations in cognition, personality, mood, sleep, and eating behavior, as well as neurological disorders such as depression, anxiety, autism, and chronic pain (121).

In adipose tissue, gut microbiota controls adipose tissue expansion as well as the onset of low-grade inflammation via mechanisms associated with gut barrier dysfunctions and metabolic endotoxemia, evidenced by an increase in plasma lipopolysaccharide (LPS), which is one of the triggering factors for inflammation and insulin resistance (122).

In muscle, studies have shown that GF mice are protected from diet-induced obesity at least in part by two mechanisms that lead to increased fatty acid catabolism in muscle (100). During exercise, GF mice have a shorter endurance swimming time, lower weight of muscle, liver, brown adipose, and epididymal fat pads, and lower serum glutathione peroxidase and catalase levels than conventional (CV) mice (123), highlighting the importance of gut microbiota in exercise performance and its potential action through the antioxidant enzyme system in athletes.

In lung, there has been emerging pathogenic links between microbiota and the gut-lung axis. Specifically, changes in microbial composition and functions in the respiratory tract and intestine may lead to alterations in immune responses and the subsequent development of lung diseases such as asthma and respiratory infections (124). During development, the “Hygiene Hypothesis” states that newborns that are delivered by caesarian section or raised in an overly clean environment are more susceptible to pediatric asthma and allergic diseases. Epidemiologic studies have suggested that the common feature of the increases risk of allergy is at least partially due to the perturbation in the founding and early development of a child’s gut microbiota (125). Conversely, allergic airway inflammation can reduce gut microbial diversity, whereas D-tryptophan produced from probiotic supplement does the opposite (126).

In bone, it has been demonstrated that colonization of adult GF mice with gut microbiota from CV mice increases both bone formation and resorption (103). This effect was time-specific, in that bone mass was reduced in the short-term, whereas in the long-term bone formation and growth plate activity were increased to promote longitudinal and radial bone growth. Nutritional interventions targeting gut microbiota have also suggested as new therapeutic options to treat inflammatory rheumatic disease (127).

Regarding kidney and the cardiovascular system, depletion of gut microbiota has been shown to protect against renal ischemia-reperfusion injury in mice (128); gut microbiota and

gut-derived hormones also modulate kidney functions and blood pressure, which are two leading risk factors for cardiovascular disease.

VII. Therapeutic potentials

Gut microbiota may be modulated in various ways to prevent and treat liver diseases. The critical role of the gut microbiota in liver disorders is supported by accumulating evidence that several complications of severe liver diseases are efficiently treated by various prebiotics, probiotics and antibiotics. Prebiotics are nondigestible carbohydrates promoting the beneficial changes of gut microbiota. Lactulose is a well-studied prebiotic commonly used for treating hepatic encephalopathy. The use of lactulose in cirrhosis patients showed divergent results. Probiotics, which are living microorganisms that present a health benefit for the host, are also commonly studied to treat liver diseases. There are varying results of the effect of probiotics (*Lactobacillus*, *Bifidobacterium*, or a probiotic combination VSL#3) in NAFLD treatment, and larger clinical trials are needed. Bifidobacteria has been shown to decrease liver injury in males with alcoholic psychosis and VSL#3 improves liver function in cirrhotic patients (129). Probiotics are effective in treating hepatic encephalopathy by decreasing ammonia production. Moreover, mitigation of NAFLD, NASH, and hepatic encephalopathy was recently found by using symbiotics, which are combination of prebiotics (such as fructo-oligosaccharides, lactulose, and inulin) and probiotics (mostly *Lactobacilli*, *Streptococci*, and *Bifidobacteria*) (129). Patients with cirrhosis and hepatic encephalopathy benefit from antibiotics, such as Rifaximin, but it is unclear whether these benefits are via modulation of gut microbiota (129). Fecal microbiota transplant is widely accepted as a therapy for recurrent *Clostridium difficile* infection, but there is a lack of clinical trial for evaluation of fecal transplant for liver diseases. In terms of bacterial metabolite, UDCA, which is a secondary BA, has been used for many years in treating cholestatic disorders, such as gallstone disease and primary biliary cirrhosis.

Conclusion

There have been extensive reports on the connection between gut bacteria overgrowth and the pathogenesis of extra-intestinal diseases, and the importance of microbial metabolites as mediators of multi-organ communication has become increasingly appreciated. However, our etiological understanding remains limited and rarely reaches the level of individual bacterial strains or specific metabolites. Utilization of recent technological advancements including metagenomics sequencing and metabolomics will greatly advance context-specific knowledge on the prevalence of bacterial strains as well as on bacterial enzymes essential for metabolite synthesis. In addition, despite growing evidence for prebiotics and probiotics as effective treatment for many diseases, the lack of a generality for different strains in experimental animals and the lack of large cohort and long-term clinical trials necessitate further studies. It needs to be established in the future how manipulation of the gut microbiota might be beneficial for the treatment of patients with various liver diseases at different disease stages.

Acknowledgments

This work was supported by National Institutes of Health grants ES025708, GM111381, ES019487, and the University of Washington Center for Exposures, Diseases, Genomics, and Environment (P30 ES007033), as well as the Murphy Endowment.

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Table 1

Bacterial metabolites, co-metabolites, and other microbial constituents as modulators of extra-intestinal function and diseases

Bacterial metabolites	Function	Action Site	Diseases	References
BAs	Dietary fat and lipid-soluble vitamins absorption; glucose and lipid metabolism; inflammation	Liver	ALD	(46, 130, 131)
		Liver	NAFLD/NASH	(41–45, 47, 51)
		Liver	Cirrhosis	(28, 51)
		Liver	PSC	(52)
		Liver	HCC	(53–55)
	Energy expenditure	Muscle, adipose	Obesity, diabetes	(50)
SCFAs	Satiety	CNS	Obesity, diabetes	(28)
	Glucose and lipid metabolism	Liver	Obesity, diabetes	(63, 64)
	GI hormone secretion; glucose metabolism;	Adipose, muscle	Obesity, diabetes	(65, 66)
Choline metabolites	Glucose and lipid metabolism	Liver	NAFLD	(28, 57, 70, 71)
	TMAO	Heart	Cardiovascular diseases	(70)
Indole-derivatives	Modulate neurotransmitter level; inflammation	Brain	Inflammatory injury	(56)
	Inflammation	Liver	Hepatic encephalopathy	(63)
	AhR activation	Liver	Impaired xenobiotic metabolism	(73, 74, 76)
Ethanol	Lipid metabolism; inflammation	Liver	NAFLD/NASH	(78–83)
LPS	Inflammation	Liver	NAFLD/NASH	(86–90, 132, 133)

Table 2

Host hormones that are altered by gut microbiota

Host hormones	Functions	Regulation by gut microbiota	References
T-βMCA	FXR antagonist	Increases in GF mice	(92)
GLP-1	Stimulate insulin secretion and inhibit glucagon secretion	Increase in GF mice	(97, 98)
Fiaf	Lipoprotein lipase inhibitor that suppresses deposition of triglycerides in adipocytes	Increases in GF mice	(99)
Bndf	Supports the survival, growth and differentiation of neurons, long-term memory	Reduces in GF mice	(101)
IGF-1	Promote bone growth	Increases by colonization of GF mice with CV gut microbiota	(102)