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The Role and Mechanism of Intestinal Flora in Blood Pressure Regulation and Hypertension Development

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Abstract

Significance: Hypertension (HTN) has a complex etiology that is characterized by genetic and environmental factors. It has become a global health burden leading to cardiovascular diseases and kidney diseases, ultimately progressing to premature death. Accumulating evidence indicated that gut microbiome was associated with metabolic disorders and inflammation, which were closely linked to HTN.

Recent Advances: Recent studies using bacterial genomic analysis and fecal microbiota transplantation as well as many lines of seminal evidence demonstrated that aberrant gut microbiome was significantly associated with HTN. The intestinal microbiome of both patients and animals with HTN had decreased bacterial diversity, disordered microbial structure and functions, and altered end products of fermentation. Gut dysbiosis and metabolites of the gut microbiota play an important role in blood pressure (BP) control, and they are therefore responsible for developing HTN.

Critical Issues: This study aimed at focusing on the recent advances in understanding the role played by gut bacteria and the mechanisms underlying the pathological milieu that induced elevated BP and led to HTN pathogenesis. Potential intervention strategies targeting the correction of gut dysbiosis to improve HTN development were summarized.

Future Directions: Larger numbers of fecal transplants from participants with HTN should be carried out to examine the magnitude of BP changes with the replacement of the gut microbiome. The proposed mechanisms for the gut in regulating BP remain to be verified. Whether intervention strategies using probiotics, dietary interventions, bacteriophages, and fecal transplants are feasible for individuals with HTN remains to be explored. *Antioxid. Redox Signal.* 34, 811–830.

Keywords: hypertension, blood pressure, gut microbiota, metabolism

Introduction

Hypertension (HTN) is one of the most prevalent cardiovascular diseases and the leading risk factor for cardiovascular and cerebrovascular complications. Various diseases such as a transient ischemic attack, stroke, retinopathy, peripheral vascular disease, renal failure, left ventricular hypertrophy, heart failure, and coronary heart disease are known to result from HTN (38). Despite the established methods for HTN diagnosis and advanced therapeutic approaches for antihypertensive treatment, the incidence rate of HTN continues to increase, and fewer than 45% of patients with HTN have well-controlled blood pressure (BP) (136).

In the past decades, a number of researchers devoted themselves to elucidating the pathogenesis of HTN. To date, many clinical and experimental observations have taken genetic and environmental factors and their interaction into account to explain HTN development (58, 69, 109). A substantial contribution of genetic components in HTN has been revealed by robust evidence using genome-wide association studies.

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Currently, the potential role of another genome, the intestinal microbiome, has gained great attention. The intestinal tract is populated with a vast number of microbes, with at least 1000 prevalent species, and serves as a special organ in the human body (59). The microbiome participates in human health and disease through interacting with the host. The effect of this community of commensal bacteria that lives within the gut on the health status of the host has been widely investigated. Biomarkers and pathophysiological mechanisms of multiple diseases, such as colorectal cancer, liver cirrhosis, arthritis, type2 diabetes, autism, and atherosclerosis, have all been linked to gut microbiota (GM) (52, 99, 100, 112, 135, 156).

A growing number of investigators focused on the role of GM in HTN. Emerging evidence characterized the GM in both patients and animal HTN models (24, 61, 79, 150). In a small cohort of patients with essential HTN, lower richness and diversity of gut bacteria was observed (150); in overweight and obese pregnant women, the butyrate, produced in GM, negatively correlated with BP (33). As for the spontaneously hypertensive rat (SHR) and angiotensin II (Ang II) infusion model of HTN, aberrant gut microbial community with increased Firmicutes/Bacteroidetes (F/B) ratio, lower microbial richness, and less acetate- and butyrate-producing bacteria was documented (150).

Meanwhile, researchers confirmed a decrease in bacterial diversity and butyrate production in rats with hypertensive obstructive sleep apnea (OSA) on a high-fat diet (24). Prominent differences in microbiome were also observed between Dahl salt-sensitive (S) and Dahl salt-resistant (R) rats (79). In addition, the disordered gut microbiome was described systematically and comprehensively in both pre-HTN and primary HTN. The causal role of gut dysbiosis contributing to HTN pathogenesis was further explored by fecal microbial transplantation using germ-free (GF) mice (61). As the understanding of the relationship between intestinal microbiome and HTN deepened, some possible underlying mechanisms were proposed, including the short-chain fatty acid (SCFAs) signaling, triangular interaction among brain–gut–bone marrow, and inflammation (97, 110, 111).

In addition to evidence showing a disordered GM structure and composition in hypertensive cohorts and experimental models, dysbiosis of microbial function and metabolic profile have been demonstrated, the causality between GM and HTN has been confirmed, and regulatory mechanisms of microbial products during BP elevation have been explored. Therefore, this study aimed at providing a summary of the recent progress on important aspects of GM during the development of HTN.

Antibiotic Use Suggests the Involvement of Gut Flora in BP Control and HTN

Antibiotic use is the most widely known way to shape the composition of GM or even deplete the intestinal commensal microbiota indiscriminately. Evidence for the influence of antibiotics on host BP could be traced back to the early 1970s. Multiple antibiotics, including erythromycin, oleandomycin, spiramycin, and leucomycin, have been demonstrated to exhibit a remarkable and sustained suppressing effect on the BP of experimental dogs, although this function of antibiotics was thought to be due to histamine release (133). By oral administration of neomycinor vancomycin, the investigators further confirmed an attenuating effect of antibiotics on experimental HTN (40) although kanamycin and amikacin were not associated with systemic BP (13).

In human patients with resistant HTN, treatment with a broad-spectrum antibiotic was reported to significantly lower the BP level and modification of GM was speculated to be responsible for the underlying mechanism (98). Nevertheless, in pregnancy-induced HTN, the association of antibiotic use in BP control was quite controversial. A reduction in the incidence of HTN during pregnancy was believed to be induced by antibiotic (*e.g.*, spiramycin) treatment (123). On the contrary, a higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) in pregnancy was also observed with antibiotic use (94). Larger prospective studies and randomized trials on antibiotic use during pregnancy-induced HTN are necessary to illuminate the role of antibiotics for hypertensive disorders in pregnancy.

A broad-spectrum antibiotic, minocycline, was shown to produce an impressive decrease in BP through rebalancing the dysbiotic GM composition in a hypertensive animal model (150). Moreover, depleting GM by antibiotic (*e.g.*, polymyxin B and neomycin) administration dramatically ameliorated gut barrier disruption, renal injury, and BP elevation induced by high salt intake (43).

Although the aforementioned findings were inspiring (Fig. 1), these antibiotics eliminate gut flora indiscriminately instead of specifically, which is of concern. Researchers argue that since beneficial commensal bacteria are abolished by antibiotic administration along with the pathogenic bacteria, the disparate effects of antibiotics on HTN should be investigated individually. For instance, antibiotics such as minocycline and vancomycin, but not neomycin, were demonstrated to lower the SBP in the SHR model (28), whereas treatment with antibiotics (*e.g.*, neomycin, minocycline, and vancomycin) resulted in elevated BP level in Dahl S rats (28).

Although the safety and efficacy of antibiotic treatment to HTN are still under investigation, the effects of antibiotics on BP are accompanied by significant alterations in GM. These findings suggest that GM is, undoubtedly, implicated in BP regulation and HTN. This raises the question of how GM is altered under hypertensive conditions and how it may be manipulated to prevent HTN.

Disordered Intestinal Patterns Are Associated with BP Level and HTN

Shift of GM composition in hypertensive animal models

Experimental animals infused with Ang II were widely known to exhibit extremely high BP and develop HTN. Raizada and colleagues (150) revealed that the dysbiotic GM structure is also a result of chronic Ang II stimulation. Lower bacterial load with decreased microbial richness and diversity, and an increased F/B ratio with a relatively higher abundance of Firmicutes and a lower abundance of Bacteroidetes were identified in rats administered with Ang II (150). Further, gut genera that function as acetate- and butyrate-producing bacteria were also depleted by Ang II (150).

An altered intestinal microbiome showing decreased alpha-diversity and distinct clustering in beta diversity in AngII-induced HTN was further confirmed recently (115). Alterations in gut microbial communities and taxonomic

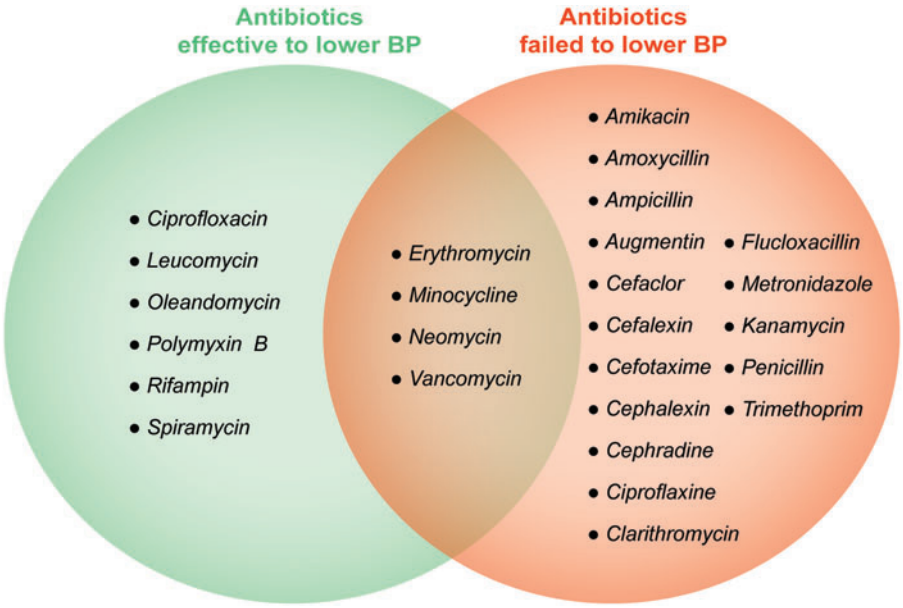


FIG. 1. Role of antibiotic usage in BP control. Antibiotics that are effective in suppressing the BP level of the host are shown in the *green circle*. Antibiotics that have been proved not to be associated with BP or even lead to higher BP are shown in the *red circle*. The overlapping area in the Venn diagram shows the antibiotics that exhibit controversial effects on BP, either effective or ineffective in lowering BP in different studies. BP, blood pressure. Color images are available online.

groups of bacteria were demonstrated after Ang II treatment. For example, the phylum Proteobacteria and the genera *Parabacteroides* and *Blautia* were significantly enriched in AngII-treated mice, whereas *Ruminococcus* and *Oscillospira* were almost completely abolished (115).

Consistent with the Ang II model, significant fecal microbial dysbiosis was also observed in the SHR HTN model. An obvious reduction in gut bacterial load showing drastically decreased microbial richness, evenness, and diversity was found in the SHR model (150), which was quite similar to the alternations in the Ang II model. Moreover, the distinct composition of the fecal microbial communities from SHR has been identified as an imbalanced F/B ratio, a reduction of acetate- and butyrate-producing bacteria, and an accumulation of lactate-producing bacteria such as *Streptococcus* and *Turicibacter* (150).

In contrast, a recent study suggested sustained alteration of GM in SHR after captopril treatment, with an increase in alpha-diversity parameters, including Chao 1 richness, observed operational taxonomic units, evenness, Shannon diversity, and Simpson diversity, and a reduction in F/B ratio (148). In another study, researchers failed to identify an altered F/B ratio in spontaneously hypertensive rat stroke-prone (SHRSP) rats, and the alpha-diversity of gut flora from Chao1 and Shannon indices was comparable to that of controls (118).

Nevertheless, shifts in the intestinal taxa have been indicated to be strongly associated with the BP level in SHR. The families Odoribactereae and Clostrideaceae, and the genera *Odoribacter* and *Clostridia* subcluster XIVa, which serve as butyrate-producing bacteria, correlated with low BP levels (1, 39, 126). *Holdemania* together with *Co-probacillus*, which are acetate-producing genera, negatively correlated with SBP (1). A positive relationship was identified between the abundance of the lactate-producing genus *Lactobacillus* and BP levels (1). Further, *Blautia* and Peptococcaceae were associated with high SBP (126).

High salt intake, a substantial risk factor for the development of HTN, has been recognized as a crucial contributor to alterations in global GM composition. The bacterial phyla Bacteroidetes, S24-7 and Veillonellaceae were shown to be more abundant in salt-sensitive animals (79); the effect of a high-salt diet on GM was further confirmed by an elevation of *Erwinia*, Christensenellaceae, Corynebacteriaceae, *Alistipes*, Ruminococcaceae *UCG 009*, and *Parasutterella* spp. and a reduction of *Anaerostipes*, *Lactobacillus*, *Oscillibacter*, *Pseudoflavonifractor*, *Clostridium* subcluster XIVa, *Johnsonella*, and *Rothia* (8, 159).

In particular, the depletion of *Lactobacillus murinus* in response to high-salt consumption has gained great attention and interest (68, 140). Although *L. murinus* from mouse feces was not detected in human samples, it can be significantly inhibited by salt concentrations *in vitro* (140). Other *Lactobacillus* species may also be sensitive to high salt in a hypertensive model.

Dysbiosis of the fecal microbiota profile has been uncovered gradually in other experimental animal models of HTN as well, including OSA and prenatal androgen-driven HTN in rats. An increase in the F/B ratio; abundance of Nocardiaceae and Clostridiaceae; and a concomitant decrease in the microbial diversity and abundance of *Akkermansia*, *Bacteroides*, *Lactobacillus*, *Clostridium*, and the taxa that are essential for producing butyrate were associated with high BP (24, 117) (Fig. 2).

Possible role of HTN-prone genes in the intestinal microbiome

Essential HTN is known to be partly caused by genetic factors. HTN-prone genes are candidate genes that may be linked to BP regulation and regarded as markers for the risk of HTN onset. Evidence suggested an interaction between HTN-prone genes and GM. For example, the genetic variation of angiotensin I converting enzyme (peptidyl-dipeptidase A) 2 (*ACE2*) was previously reported to be associated with HTN (71, 93). Further, the *ACE2* mutant has been documented to alter the composition of intestinal microbiota (36). Besides, a recent study demonstrated that the G protein-coupled estrogen receptor, as a host genomic factor, plays a role in promoting microbiota alterations that contribute to vascular dysfunction

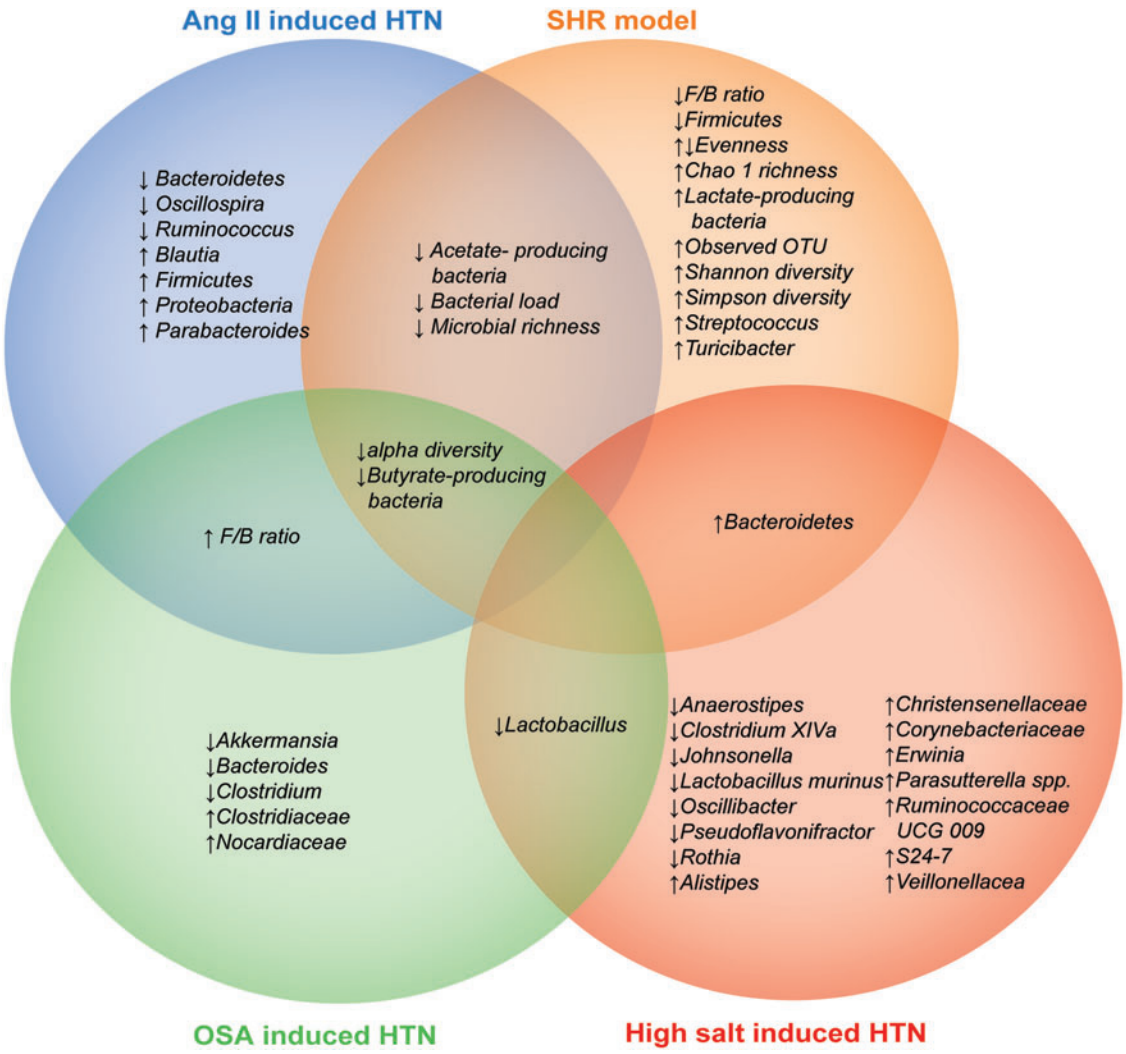


FIG. 2. Shifts of the fecal microbiota profile in hypertensive animal models. The Venn diagram shows the features of dysbiotic GM structure that have been associated with different hypertensive animal models. The *blue circle* indicates the alterations of GM in animals with Ang II-induced HTN. The *orange circle* shows the significant fecal microbial dysbiosis in the SHR model. The *green circle* indicates the dysbiosis of the fecal microbiota profile in the OSA-induced hypertensive animal model. The *red circle* indicates alterations of global GM composition in high salt-induced HTN. The overlapping area in the Venn diagram shows the common features of GM shared in different hypertensive animal models. The *upward arrows* indicate an increase, whereas the *downward arrows* indicate a decrease. Ang II, angiotensin II; F/B, Firmicutes/Bacteroidetes; GM, gut microbiota; HTN, hypertension; OSA, obstructive sleep apnea; SHR, spontaneously hypertensive rat. Color images are available online.

and regulate BP (132). This information increases the possibility that HTN-prone genes may play a role in HTN onset partly through modulating GM.

Dysbiotic microbes in the gut of patients with HTN

Detailed information on the changes in the GM profile of populations subject to primary HTN has been obtained (Fig. 3). Lower bacterial Chao richness, Shannon diversity, and Pielou's evenness were initially identified in 7 patients with high SBP compared with 10 healthy controls (150).

In a larger cohort of human patients with HTN, the dysbiotic pattern of gut bacteria was further elucidated. A previous study revealed the fecal microbial features of 41 controls, 56 individuals with pre-HTN, and 99 individuals with HTN, comprehensively based on metagenomic analyses (61). Consistent changes in the GM structure, including decreased number of genes and much lower alpha-diversity, were confirmed in patients with HTN. An imbalanced gut enterotype distribution trending toward *Prevotella* was also observed. The prevalence of bacteria such as *Prevotella*, *Klebsiella*, *Porphyromonas*, and *Actinomyces* was overrepresented; whereas *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, *Coprococcus*, and *Butyrivibrio* were reduced in patients with HTN (61).

A subsequent study on 60 patients with HTN and 60 matched controls showed lower gene count, reduced diversity, and altered microbial composition, which were consistent with the previous findings (145). Again, an enrichment of *Proteobacteria*, *Klebsiella*, *Streptococcus*, *Clostridium*, *Parabacteroides*, *Eggerthella*, and *Salmonella*, and a reduction in

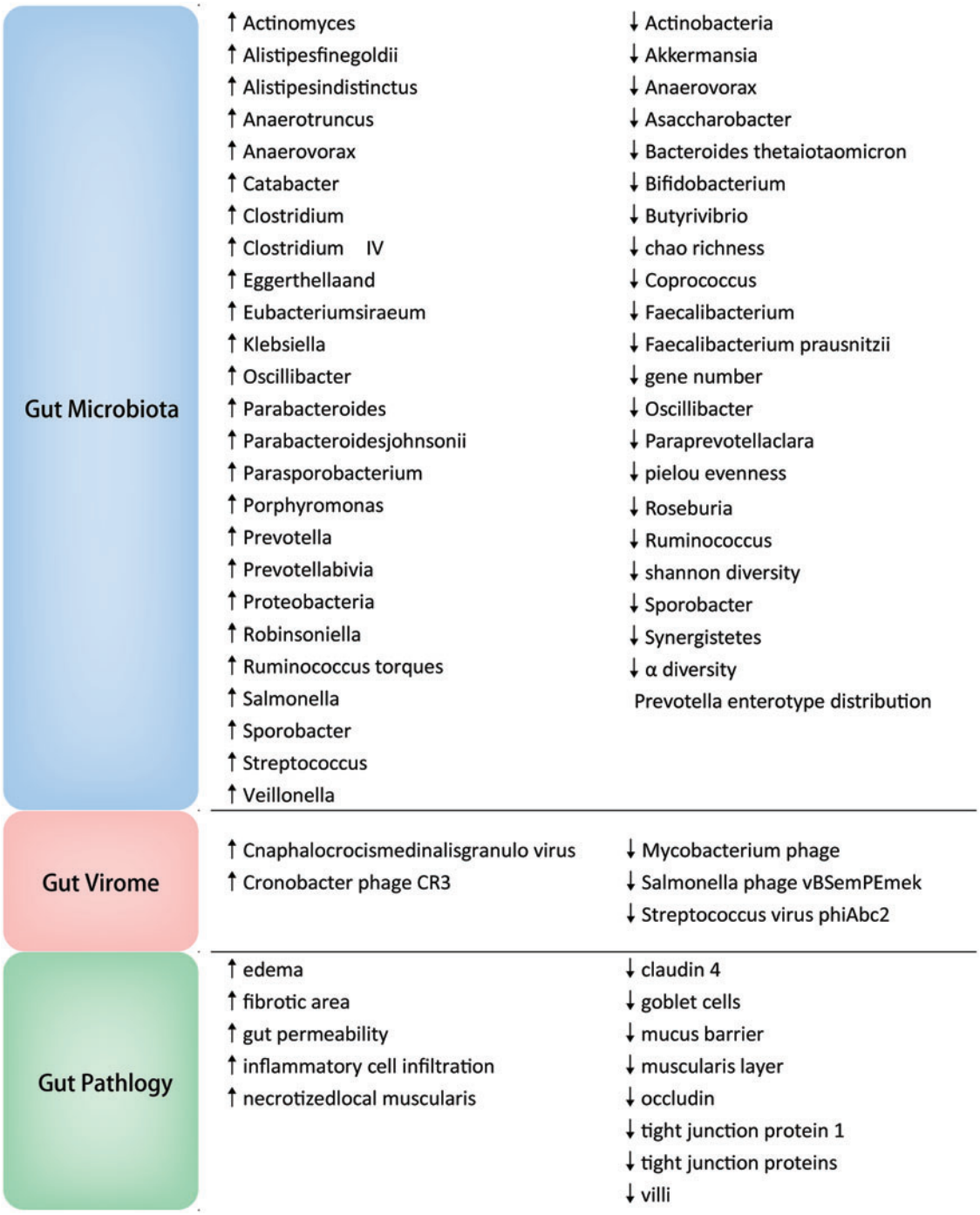


FIG. 3. Dysbiotic gut microbes, gut virome in patients with HTN, and the pathological alterations in hypertensive gut. The *blue area* shows how the GM profile changes in populations subject to HTN. The *pink area* indicates changes of the gut viral communities in hypertensive patients. The *green area* shows alterations in the gut epithelial integrity and wall pathology that are linked to HTN. The *upward arrows* indicate an increase, whereas the *downward arrows* indicate a decrease. Color images are available online.

the prevalence of *Actinobacteria*, *Synergistetes*, *Roseburia*, and *Faecalibacterium prausnitzii* were found in patients with HTN (145).

Additional evidence focusing on the correlation between GM composition and BP has been obtained in recently published studies. Distinct GM composition with a higher abundance of *Parabacteroides johnsonii*, *Klebsiella*, *Anaerotruncus*, *Eubacteriumsiraeum*, *Alistipesindistinctus*, *Prevotellabivia*, *Ruminococcus torques*, and *Alistipesfinegoldii*, and a lower abundance of *Bacteroides thetaiotaomicron* and *Paraprevotellaclara* were significantly associated with SBP (54).

In 529 participants from the Coronary Artery Risk Development in Young Adults study, HTN and SBP were inversely associated with genus richness and Shannon diversity (119). Positive associations were demonstrated between HTN and genera *Veillonella*, *Anaerovorax*, *Clostridium*

cluster IV, *Oscillibacter*, *Sporobacter*, *Catabacter*, *Robinsoniella*, and *Parasporobacterium*; whereas *Akkermansia*, *Ruminococcus*, *Anaerovorax*, *Sporobacter*, and *Asaccharobacter* tended to be found in individuals with lower SBP (119).

In addition, fecal bacteria in the human intestine have been investigated in age-, sex-, ethnic background-, pregnancy-, and OSA-associated HTN. In elderly patients with HTN, the abundance of Betaproteobacteria, Burkholderiales, Alcaligenaceae, Faecalibacterium, and Ruminococcaceae diminished; whereas that of *Escherichia coli*, Lachnospiraceae–*Eubacterium_hallii_group*, Lachnospiraceae–*Lachnoclostridium*, Lachnospiraceae–*Blautia–Ruminococcus_sp__5_1_39BFAA*, and Ruminococcaceae–*Faecalibacterium* increased in participants with reduced exercise capacity (154). Thus, altered GM may potentially contribute to the pathogenesis and progression of reduced exercise capacity in elderly patients with HTN.

Considering that the prevalence of HTN is much higher in men compared with women until the age of 65 years (7), the possible relationship between the fecal microbiome and sex differences in HTN was recently discussed by Beale *et al.* (5). Although distinct GM has been widely recognized in women and men (9, 85, 91, 116), the evidence directly linking GM and sex differences in BP is quite scarce, and the role of GM in sex-dependent HTN is still a hypothesis. Issues regarding the difference in the intestinal microbial signature of women and men with HTN remain to be addressed in future studies.

Regarding ethnic backgrounds in HTN, black and white Americans are known to experience a different incidence and severity of high BP (138), and ethnic-specific microbiota profiles have suggested that ethnic origin is an important factor for differences in the composition of fecal microbiota (21). A study on a small cohort consisting of 20 African Americans and 33 white Americans confirmed unique GM structures in black and white patients with HTN (26, 134). The differences in gut microbial taxonomy were suggested to be dependent on the race of patients with HTN, although the study was limited by very small sample size.

In obese pregnancy-induced HTN, although studies failed to observe differences in the F/B ratio, increased SBP and DBP was associated with altered GM composition (33), and the presence of several bacteria inversely correlated with SBP. The abundance of Odoribacteraceae, Clostridiaceae, and Christensenellaceae families; the *Blautia* genus; and the butyrate-producing genus *Odoribacter* negatively correlated with HTN. Further, disease-related dysbiosis in GM was reported most recently in patients with varying severities of OSA–hypopnea syndrome (OSAHS) (56). The oral microbiota in OSAHS-related HTN was characterized in a cohort from South China (55). However, whether a distinct gut flora composition exists in populations with HTN and OSAHS and how the taxa are associated with high BP under OSAHS remain largely unknown.

HTN, as one of the most prevalent cardiovascular diseases, is also a leading risk factor for other cardiovascular and circulatory diseases. Various diseases induced by HTN such as stroke, retinopathy, peripheral vascular disease, renal failure, heart failure, coronary heart disease, and atrial fibrillation are all known to be associated with alterations in the microbiota that colonize the gastrointestinal tract (12, 19, 27, 57, 67, 108, 157, 162). The GM signatures of these diseases are being identified by an increasing number of studies.

Dysfunctional intestinal environment of gut virome and pathology is implicated in HTN

Viral communities are another important member of the enteric environment. The viral component of the microbiome is mainly composed of bacteriophages, which may interact with the GM, and even kill or deplete the bacteria (131). The presence or absence of a specific viral species could lead to the alteration of their bacterial hosts in the intestine, and eventually perturb the human host, similar to a butterfly effect. Dynamic changes in the human gut virome in response to diet and the early years of life have been identified (64, 80). The healthy gut virome in humans is composed of common bacteriophage communities, which play a crucial role in balancing the GM and maintaining human health (76). Type 2 diabetes, Crohn's disease, and ulcerative colitis were linked to gut virome with increased bacteriophage richness and expansion in Caudovirales, Microviridae, Podoviridae, and Siphoviridae (74, 90).

Most recently, using the whole-community metagenomic sequencing dataset of 196 fecal samples from a previous study (61), investigators examined the changes in the gut virome in patients with pre-HTN and HTN (Fig. 3) (35). Although viral diversity in HTN was unchanged, a shift in the viral community, including decreased *Streptococcus virus phiAbc2*, *Salmonella phage vBSemPEmek*, and *Mycobacterium* phage, and increased *Cronobacter phage CR3* and *Cnaphalocrocismedinalisgranulovirus* in pre-HTN and HTN were identified. The linkages between gut viruses and bacteria suggest an important role of gut virome that may contribute to bacterial dysbiosis in HTN.

Gut epithelial integrity and wall pathology are quite essential for maintaining the physiological function of intestinal environments, and increasing evidence demonstrates pathophysiological alterations in the gut of animals with HTN. Enhanced gut permeability as a result of the lower expression level of tight junction proteins, such as occludin, tight junction protein 1, and claudin 4, was observed in experimental animals with HTN (Fig. 3) (47, 103, 111). Moreover, increased fibrotic area, thicker muscularis layer, shorter and stunted villi, and fewer goblet cells were revealed in the small intestine of Ang II animals and SHR.

Consistent findings in a model of OSA-induced dysbiosis were recently obtained. The OSA was confirmed to cause significant loss in the number of epithelial goblet cells, which served as mucus-producing cells and limited the proximity of luminal bacteria to the epithelium (29). The gut wall damaged by OSA was, thus, equipped with a thinner mucus barrier that failed to protect the underlying epithelium from luminal bacteria translocation. Under the pressure of high-salt diet, the lamina propria of the small intestine displayed more edema demonstrated by increased gap, more necrotized local muscularis, decreased mucosal thickness, and more inflammatory cell infiltration between the mucosalglands (159).

The damaged gut wall and increased permeability of the gut epithelial barrier is extremely likely to contribute to an inflammatory status, which is susceptible to various stimuli that lead to BP elevation. Although the linkage of intestinal epithelial barrier dysfunction and HTN in human patients with high BP has been recently confirmed (54), whether a shift in gut microbial genera is the reason or consequence of gut pathological changes remains unclear. This should be emphasized in future investigations.

Connectivity of Gut Bacterial Function and Host Metabolism in HTN

Altered bacterial function due to gut dysbiosis

The damaged state of the gut, especially the colonizing bacteria, may exhibit impaired metabolic functions that link to host biology in HTN. Metabolic pathways associated with lipopolysaccharide biosynthesis and export, phospholipid transport, membrane transport, phosphotransferase system, biosynthesis of phenylalanine and phosphatidylethanolamine, steroid degradation, secretion system, and cellulose-binding domains were found to be dominant in the hypertensive gut microbiome (61, 145). A concomitant depletion in microbial functions involved in host glycan using enzymes, branched-chain amino acid biosynthesis and transport, ketone body biosynthesis, two-component regulatory system, and degradation of methionine and purine were observed in HTN (61, 145). Given the predicted metabolic function of GM based on the Kyoto Encyclopedia of Genes and Genomes database in HTN, it was then possible that these changes in microbial metabolism altered host metabolism.

Changes in metabolic profiles linked to BP

The relationship between global metabolic profiles and HTN (Fig. 4) has been defined by 1H nuclear magnetic resonance (NMR) spectroscopy, gas chromatography–mass spectrometry, and NMR spectroscopy (10, 63). Serum metabolic perturbations in patients with HTN include betaine, mevalonic acid, corticosterone, beta-leucine, propionic acid, methionine, D-glucose, glycine, tyrosine, and malic acid (63). The change in metabolic patterns of patients with HTN was revealed by using high-throughput liquid chromatography–mass spectrometry. Small-molecule metabolites in human serum were identified to be related to BP. For example, *N*α-acetyl-L-arginine, stearic acid, phosphatidic acid, and glucoside were abundant in HTN samples, but phosphatidylserine, 3,4,5-trimethoxycinnamic acid, lysophosphatidylcholine, *S*-carboxymethyl-L-cysteine, and lysophosphatidylethanolamine were significantly diminished (61).

Moreover, the blood metabolic profiles of hypertensive animal models were characterized by an elevation of 3-hydroxybutyric acid, oleic acid, hexadecanoic acid, linoleic acid, lysine, beta-sitosterol, and stearic acid, and a deficiency of homoserine, threonine, phenylalanine, erythrose, beta-D-methylglucopyranoside, alpha-tocopherol, non-esterified cholesterol, and butyrate (72, 149).

The metabolic profile of urinary metabolites was also found to be significantly associated with BP in a randomized controlled study. *N*-methyl-2-pyridone-5-carboxamide, tryptophan metabolism in the urine inversely correlated with BP (70). Gut microbial co-metabolites such as hippurate, 4-cresyl sulfate, and pheny-lacetylglutamine, and other urinary metabolites (proline-betaine and carnitine) were linked to HTN (70).

Recently, salt-responsive metabolites in HTN were identified in either serum or stool. Lower circulating levels of 3-hydroxybutyric acid and the ketone body beta-hydroxy butyrate were detected in high-salt-fed rats with HTN (14). Further, a high-salt diet reduced the levels of indole-3-lactic acid and indole-3-acetic acid in feces (140). In patients with HTN, altered GM metabolites were found in feces, including hexacosanedioic acid, palmitoyl-L-carnitine, phosphocholine, palmitic acid, oleamide, linoleic acid, 6-hydroxynicotinic acid, L-leucine, pantothenic acid, and vitamin D3 (163), contributing to the understanding of host–bacteria metabolic interaction.

Central role of GM in modulating metabolomics

Gut microbes are well known to exert metabolic functions, produce dozens of metabolites, and modulate host metabolic phenotypes. The production of circulating small-molecule metabolites, such as phenylacetate, benzoate, *p*-cresol, and indole from aromatic amino acids, is dependent on GM (6, 139, 161). In a chronic Ang II infusion model, the GM plays a central role in modulating the alteration in plasma and fecal metabolomes in response to Ang II (17). GM metabolites may play a critical role in mediating gut microbial effects on the host. The microbial products would directly interact with host organs to contribute to host biology and affect health and disease progression. For example, the production of tryptophan-derived indole by intestinal bacteria exerted anti-inflammatory effects and improved the development of chronic liver diseases (37).

Variation in bacterial community members is associated with the dynamics of host metabolic pathways and altered small-molecule metabolites. Specific urinary metabolites, including dimethylamine, taurine, lactate, glycine, 2-hydroxyisobutyrate, glycolate, 3,5-hydroxylbenzoate, and 3-aminoisobutyrate, were linked with a key functional member of the gut microbiome, *F. prausnitzii* (62). Other gut microbial co-metabolites such as phenylacetylglutamine, 4-cresol sulfate, and 4-hydroxyphenylacetate were predicted to be correlated with *Subdoligranulum* and *Bifidobacterium pseudocatenulatum* (62). In patients suffering from coronary artery disease, a relationship between certain gut bacteria and host metabolic pathways such as taurine, sphingolipid and ceramide, and benzene metabolism was reported (67).

A previous study found that decreased trichloroethanol glucuronide correlated positively with *Bifidobacterium* and *Akkermansia* and negatively with *Prevotella* in patients with HTN (61). The accumulation of stearic acid in the bloodstream of individuals with pre-HTN and HTN was considered to be influenced by gut microflora due to the complicated association with *Klebsiella*, *Prevotella*, *Enterobacter*, *Bifidobacterium*, and *Roseburia* (61). However, whether these specific metabolic products were directly metabolized by certain intestinal microorganisms remained unclear. To date, little information is available regarding this issue.

Investigators have identified *Clostridium sporogenes*, a gut bacterium from the phylum Firmicutes, as a gut commensal bacterium that produces indolepropionic acid from dietary tryptophan (23). In addition, indole-3-lactic acid, indole-3-acetic acid, and indole-3-carboxaldehyde were indicated to be metabolized by *Lactobacillus* from tryptophan in salt-sensitive HTN (140, 155). These small-molecule metabolites allowed the dysbiotic intestinal microbiota to impact metabolic pathways and regulate host biology in the development of HTN.

Causality Between GM and HTN and the Proposed Mechanistic Rationale

Cause–effect relationship between intestinal microbial changes and BP

The causal role of GM in controlling BP and regulating arterial HTN was investigated by using GF mice. In the

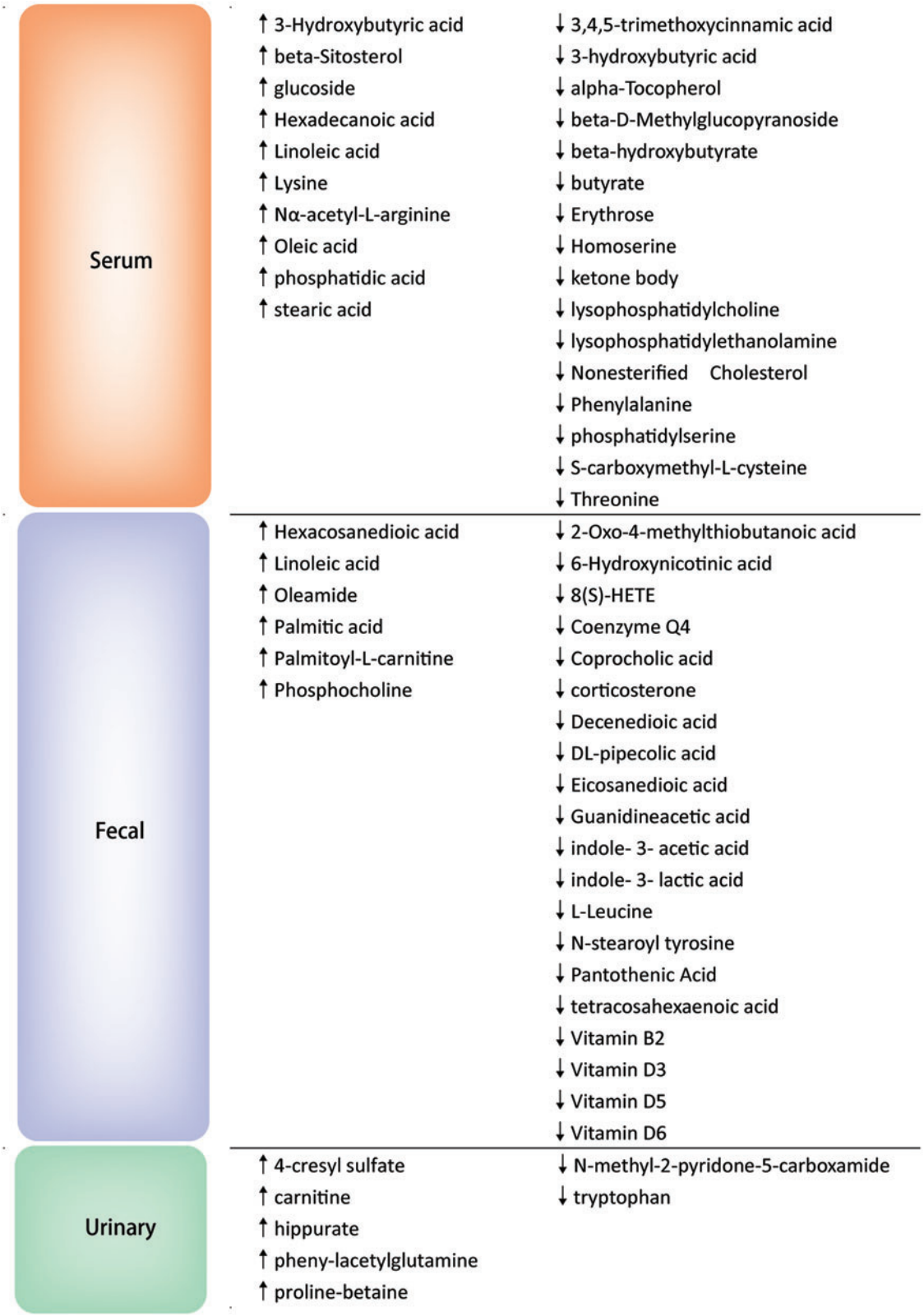


FIG. 4. Perturbed host metabolic patterns associated with HTN. The *orange area* shows global serum metabolic profiles in HTN. The *purple area* indicates altered GM metabolites in feces of HTN. The *green area* shows the metabolic profiles of urinary metabolites in HTN. The *upward arrows* indicate an increase, whereas the *downward arrows* indicate a decrease. Color images are available online.

absence of gut bacterial flora, GF mice suffering from portal vein ligation failed to develop portal HTN compared with colonized controls (84). Further, GF mice exhibited blunted systemic inflammation, vascular dysfunction, arterial HTN, and endorgan damage by Ang II induction (51). Collectively, the maintenance of high BP and the pathogenesis of HTN, at least in part, were dependent on the presence of GM.

After the critical role of GM in HTN was recognized, fecal microbiota transplantation (FMT) was performed in multiple hypertensive animal models. Several studies observed the influence of GM alterations on BP level. After GM was exchanged between SHRSP and Wistar-Kyoto (WKY) strains, significantly elevated BP was found in WKY receiving SHRSP microbiota, and lower SBP was detected in SHRSP colonized with WKY microbiota (1). In contrast, the transplantation of cecal contents from salt-sensitive rats into salt-resistant rats did not alter the SBP of the salt-resistant rats (79). However, the salt-resistant rat cecal microbiota consistently elicited increased SBP of the salt-sensitive rats, which was speculated to be due to the different genomic composition between salt-sensitive and salt-resistant rats (79).

High-fat diet and OSA are known to lead to dysbiosis and alterations of the GM. The dysbiotic intestinal flora of OSA rats on high-fat diet were verified to contribute to a hypertensive phenotype through transplantation (24). In human patients with HTN, decisive evidence was obtained for the crucial causal role of disordered human GM in triggering elevated BP by transplantation into GF mice (61).

Exchanging the GM between SHR and WKY by FMT demonstrated a crucial activity of GM as a pro-hypertensive factor to modulate the immune system and the sympathetic nervous system, affect the vascular function, and control the BP (125, 126). The cause–effect relationship between elevated BP and altered GM was further verified as restoration of a normalized intestinal microbiota protected against the development of portal HTN (30). Most recently, changes in GM and SCFAs were confirmed to contribute to HTN development in patients with preeclampsia (15).

Although most of the findings illustrating the causality between GM and HTN are based on evidence in experimental animals, a case of a human patient undergoing FMT also supported it. The FMT triggered persistent aggravation of HTN in this case, and the previously well-controlled BP of the recipient patient increased up to 200/110 mmHg post-FMT (32).

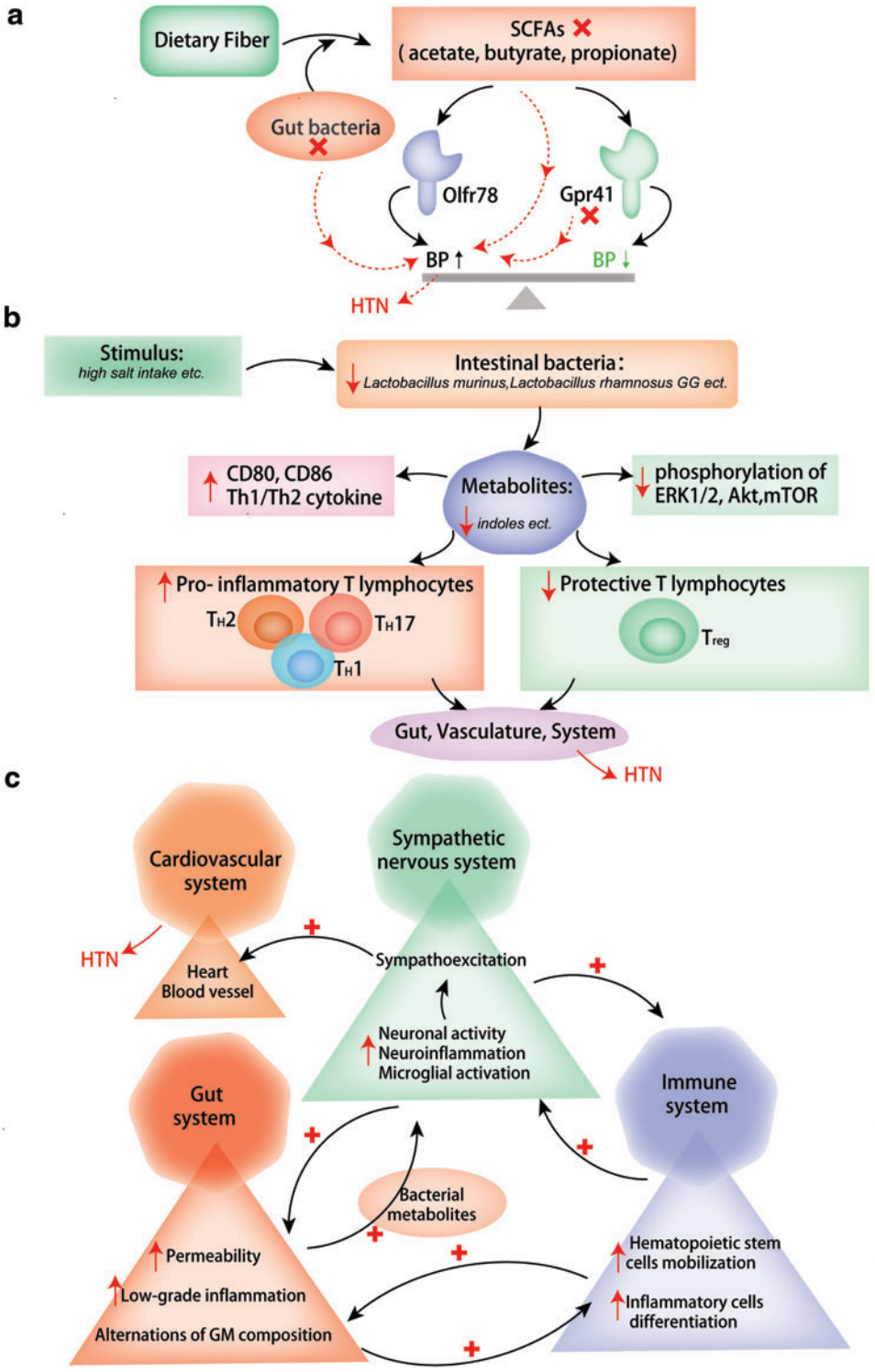
In addition, considerable evidence indicated that the gut microbial metabolites exerted an influence on BP regulation and HTN development. The SCFAs produced by the microbes inhabited in the intestine were protective against HTN (4, 77). Gut bacterial production of indole from dietary tryptophan was found to decrease the arterial BP (45). Gallic acid, a microbiotic anthocyanin metabolite, significantly attenuated BP in an experimental model of HTN (50). Trimethylamine *N*-oxide is another notable GM metabolite that correlated with a higher prevalence of HTN (31). With these findings, the direct causality of GM on BP control of the host was comprehensively demonstrated, both in humans and in animals.

Possible mechanisms linking changes in GM to BP

A growing number of researchers are focused on exploring the possible mechanism underlying the effect of GM on BP. Various theories regarding how GM contributes to HTN pathogenesis have been developed and elucidated (Fig. 5). The most salient player that mediates the contribution of GM on BP regulation is considered to be the SCFAs. The SCFAs consist of acetate, butyrate, and propionate, which depend on the fermentation of dietary fibers by the GM. The SCFAs are absorbed into the bloodstream and exert an influence on BP through two primary receptors, olfactory receptor 78 (Olfr78) and G-protein-coupled receptor 41 (Gpr41) (81, 88, 95–97). Under the stimulation of SCFAs, Olfr78 contributes to hypertensive effects, whereas Gpr41 functions to lower the baseline BP (88, 95, 97).

Considering the opposing responses of Olfr78 and Gpr41 on BP, the presence of these two receptors is quite necessary for antagonizing the function of each other and maintaining a physiological BP level after SCFA exposure. Once this balance is struck, the over-expression or deficiency of Olfr78 or Gpr41, or an imbalance in SCFAs due to alterations of gut

FIG. 5. Proposed mechanistic rationales explaining the causal role of GM for BP controlling. (a) SCFAs mediate the contribution of GM in BP regulation. Dietary fiber is fermented by the GM, thereby producing the SCFAs acetate, butyrate, and propionate. The SCFAs are absorbed into the bloodstream and act on two receptors, Olfr78 and Gpr41. The activation of Olfr78 under the stimulation of SCFAs contributes to hypertensive effects, whereas Gpr41 functions to lower the BP. The function of Olfr78 and Gpr41 on BP maintains a balanced and physiological BP level. When the gut bacteria or SCFAs or Gpr41 is blocked, BP is influenced and HTN develops. **(b)** Under stimuli such as high salt intake, intestinal bacteria such as *Lactobacillus murinus* and *L. rhamnosus GG* are depleted and the production of downstream bacterial metabolites (*e.g.*, indole) is suppressed, resulting in the activation of CD80, CD86, and Th1/Th2 cytokines, and inhibiting the phosphorylation of ERK1/2, Akt, and mTOR. Meanwhile, pro-inflammatory T-lymphocyte lineages, such as Th1, Th2, and Th17, are increased, and protective T-lymphocytes, such as Tregs, are decreased in the gut and vasculature. These actions driven by GM lead to HTN onset. **(c)** Communication between the sympathetic nervous system, immune system, gut, and cardiovascular system. Neuronal activity, neuroinflammation, and microglial activation lead to sympathoexcitation, which activates the immune system to promote hematopoietic stem cell mobilization and inflammatory cell differentiation. The activation of the immune system, in turn, positively acts on the sympathetic nervous system. The enhanced activity in the sympathetic nervous system also acts on the gut system, promotes increased gut permeability and low-grade inflammation, and alters the GM composition. The shifts in the gut system are positively fed back to the sympathetic nervous system. Similarly, the interaction between the gut system and the immune system is also a positive feedback loop. The continuously activated sympathetic nervous system due to the positive feedback loop influences the function of the heart and blood vessels in the cardiovascular system and finally leads to HTN. The *upward arrows* indicate an increase, whereas the *downward arrows* indicate a decrease. "×" means blockage. The *red dotted line* indicates alterations that would happen when blockage ("×") occurs. "+"indicates a positive effect. Gpr41, G-protein-coupled receptor 41; Olfr78, olfactory receptor 78; SCFA, short-chain fatty acid; Th, T helper; Treg, regulatory T. Color images are available online.



bacteria would influence the BP and the pathology of either HTN or hypotension would occur.

Bile acids are also key microbial metabolites that directly interplay with the host and affect BP. Primary bile acids (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol in the liver and transformed into secondary bile acids (deoxycholic acid and lithocholic acid) in the gut depending on the microorganisms (78). The GM-produced secondary bile acids then enter the circulation and affect cardiovascular functions by targeting bile acid-sensing receptors, farnesoid X-activated receptor (FXR), G-protein-coupled bile acid receptor 1 (TGR5), pregnane X receptor, vitamin D3 receptor (VDR), muscarinic acetylcholine receptors M2 and M3, and sphingosine 1-phosphate receptor 2 (S1PR2) (11). Certain bile acids have been indicated to be linked with portal HTN *via* FXR, TGR5, and S1PR2 (49, 92).

Evidence suggests that chenodeoxycholic acid reduces SBP, improves vascular relaxation, and inhibits vasoconstriction by

activating FXR (60). Besides, VDR is suggested to play a considerable role in BP regulation and HTN treatment (65), and S1PR2 antagonism has been shown to reduce the pressure in the portal vein (49). These microbial-derived bile acid metabolites are, thus, believed to participate in the GM-mediated shifts in host BP.

Another important theory widely accepted to explain the role of gut microorganisms in BP regulation and HTN development is the immune system and exaggerated inflammatory responses. Pro-inflammatory T lymphocytes such as T helper (Th)1, Th2, Th17, and protective regulatory T (Treg) cells are linked to the development of HTN and end-organ damage (75, 89, 113, 137). The induction of Th1 cells and the activation of the Th17 axis have been identified as driven by intestinal bacteria (3, 140). The feces from WKY rats effectively rescued the imbalanced Th17/Treg ratio in mesenteric lymph nodes and aorta in SHR by FMT, but feces from SHR rats increased expression levels of CD80 and CD86 and enhanced the activation and infiltration of T cells (125). T cell activation in the gut immune system and vascular T-cell accumulation have been verified to be quite necessary for the control of BP by GM (125).

High salt intake is known to reduce the prevalence of commensal microbial species and, consequently, lead to a hypertensive and proinflammatory environment. The role for the gut microbiome in mediating the effects of high-salt diet on Th17 cell differentiation and the pathogenesis of high BP has been revealed. The salt-sensitive *Lactobacillus* species and other gut flora might be responsible for this phenomenon. The salt-reduced intestinal *Lactobacillus* in the gut microbiome and depleted production of bacterial indoles have been demonstrated to promote the number of pro-inflammatory Th17 cells and increase BP in response to high salt intake (140, 143) whereas treatment with *L. murinus* prevented salt-induced HTN and activation of Th17 cells (101, 140). Another strain of GM, *L. rhamnosus* GG, was suggested to suppress the aggravation of salt-sensitive HTN by modulating Th1/Th2 cytokines and blocking phosphorylation of ERK1/2, Akt, and mTOR (68).

Recent studies depicted a capacity for autophagy in lowering BP and delaying the development of HTN (25, 102, 158). Autophagy has been proved to play a critical role in maintaining the composition and diversity of GM and modulating the interaction between GM and the immune system (82, 147). Dysfunctional autophagy is known to directly lead to gut dysbiosis. For example, the deficiency of autophagy-associated gene immunity-related GTPase M or *Atg5* would affect GM composition (107, 147). Evidence also suggested that GM could, in turn, influence autophagy in the intestine (18). Given the complicated interaction between autophagy and GM, currently it is difficult to speculate how autophagy participates in the process of GM-dependent BP control.

An increasing number of studies have reported on the causal impact of alcohol consumption on elevated BP and HTN (48, 160). Meanwhile, alterations of the intestinal microbiome are detected in both experimental animals and human patients after alcohol intake (66, 13a). The intestinal microbiome is, thus, proposed as a potential factor mediating the development of alcohol-induced HTN. Further, the genetic polymorphism associated with alcohol consumption in the acetaldehyde-metabolizing enzyme mitochondrial aldehyde dehydrogenase (*ALDH2*) gene is reported to facilitate the onset of alcohol-related HTN (44, 160). As *ALDH2* deficiency has been identified to aggravate the gut barrier disruption induced by ethanol (16), the intestinal microbial ecosystem is supposed to be responsible for the role of *ALDH2* in BP regulation.

Raizada and colleagues discussed the role of communication between peripheral and neuroinflammation, the autonomic nervous system, and bone marrow on gut permeability and HTN pathophysiology (110). A complex hypothesis of brain–gut–bone marrow connection in HTN onset was generated. On the one hand, the sympathoexcitation due to enhanced neuronal activity and neuroinflammation mobilizes hematopoietic stem cells in the bone marrow and promotes the differentiation of inflammatory cells, which, in turn, translocate back into the brain and aggravate neuroinflammation. On the other hand, the activation of the sympathetic nervous system induces permeability, low-grade inflammation, and alterations of GM composition in the gut, which, in turn, contribute to neuronal activity by releasing pathogenic bacterial metabolites into the circulation.

Direct evidence has been obtained supporting the notion that sympathetic activation leads to impaired gut epithelial integrity, followed by an increased number of inflammatory cells within the intestinal wall, and contributes to inflammation and HTN (111, 122). Further, the connection between mature inflammatory cells in the bone marrow and dysbiosis in the gut is also indicated as a positive feedback loop (110). This vicious cycle of the sympathetic nervous system, immune system, and gut system was suggested to be responsible for the development and maintenance of the hypertensive status.

Recently, new insights were proposed to explain the interaction between the brain and gut during BP regulation. Investigators suggested that the sympathetic nervous system might simultaneously impact the function of the cardiovascular system (heart and blood vessel) and the immune system (bone marrow and spleen), as well as the gut. Circulating factors such as SCFAs, endocrines, and cytokines, as well as vagal nerve signaling derived from the immune system and gut, and they were fed back to the brain circumventricular organs (151). On the contrary, this presumed mechanism behind the association between gut dysbiosis and HTN has also been suggested to maintain homeostasis and prevent HTN (151).

Moreover, microglial cell activation within autonomic brain regions has been shown to be necessary for the dysfunctional brain-gut axis during the development of HTN (115, 128). After the blockage of inflammatory activity and inhibition of microglial activation, proinflammatory cytokines in the paraventricular nucleus of the hypothalamus are depleted, accompanied by attenuation of sympathetic activity and improvement in left ventricular hypertrophy, which also restores dysbiotic gut microbial communities and protects the gut wall from pathological alterations (115).

Therefore, the complicated and bidirectional communication between the brain and the gut is derived from neurogenic inflammation and microglial cell activation in the paraventricular nucleus, which impacts the sympathetic nervous system activity, the GM, and permeability. The importance of the circuit for a leaky gut, in turn, activates the sympathetic nervous system to exacerbate the progression of HTN.

Insights on Intervention Strategies to Correct Gut Dysbiosis and Prevent HTN Development

Consumption of probiotics in BP regulation

Considering the crucial contribution of GM in BP elevation and HTN development described earlier, intervention

strategies aiming at protecting against HTN by attenuating the imbalanced gut have drawn extensive attention. A keen interest has been focused on the effective use of a wide variety of probiotic strains (20, 106, 130). The consumption of probiotics has been shown to affect BP levels of the host both in animal models and in human patients with HTN. A meta-analysis of nine randomized controlled clinical trials indicated potential effects and significant reductions in both SBP and DBP by probiotic consumption (53).

However, the potency for antihypertensive activity of probiotics depends on certain specific strains. For example, different strains of *L. plantarum* show inconsistent activity. The *L. plantarum* DSM 15313 strain was found to ferment dietary intake of blueberries and lower the SBP and DBP in *NG*-nitro-L-arginine methyl ester (L-NAME)-induced animals with HTN (2). The recombinant *L. plantarum* NC8 strain was also shown to decrease SBP in the SHR model by restoring nitric oxide and reducing endothelin and Ang II (146). However, another strain from *L. plantarum*, the HEAL19, failed to ameliorate the high BP induced by L-NAME, despite its protective effect on liver cells and influence on the cecal microbiota (144).

Even the hypotensive effect of the same strain of probiotics, for example the *L. fermentum* CECT5716, varied in different models of HTN. In the SHR model, the long-term administration of *L. fermentum* CECT5716 in drinking water reversed the impaired endothelium-dependent relaxation, abolished the increased superoxide levels, and lowered SBP (34). In rats with HTN induced by tacrolimus, *L. fermentum* CECT5716 treatment reduced vascular oxidative stress, restored the imbalanced Th17/Treg ratio in both mesenteric lymph nodes and spleen, and prevented endothelial dysfunction and HTN (127). However, in an L-NAME-induced HTN model, the development of HTN was not effectively inhibited by the probiotic *L. fermentum* CECT5716, although the gut dysbiosis, Th17/Treg balance, vascular oxidative stress, and endothelial dysfunction were slightly affected (105).

Increasing numbers of probiotics, such as *Lactobacillus* sp. and *Bifidobacterium* sp., are suggested to reduce high BP. Maternal administration of the probiotic *L. casei* has been shown to prevent against high-fructose consumption-induced HTN in the adult rat offspring (42). Intraduodenal injection of *L. johnsonii* La1 was identified to exert a hypotensive action in urethane-anesthetized rats (121). The probiotic *L. coryniformis* CECT5711, with immunomodulatory properties, could reduce high BP in obese mice (124). Oral application of a probiotic cocktail with *L. casei*, *L. acidophilus*, *L. bulgaricus*, *Saccharomyces thermophilus*, and *B. longum* also had antihypertensive activity in rats (129).

In individuals with HTN, probiotic-dependent reduction of BP and attenuation of HTN have been observed with the consumption of *L. helveticus* LBK-16H, *L. helveticus* and *S. cerevisiae*, *L. casei*, *L. casei* strain Shirota and *Lactococcus lactis* YIT 2027, and *L. plantarum 299v* (46, 83, 86, 87, 114). Given the numerous probiotics as candidates for HTN therapy, choosing a specific probiotic strain that is both safe and effective in lowering BP and preventing HTN remains a great challenge in clinical application. Individualized and precise probiotic medicine is quite important and worth exploring.

Dietary interventions and HTN

Nonpharmacological preventive strategies, including lifestyle modifications and dietary interventions, seem more acceptable and safe for patients with hypertensive cardiovascular disease. A high-fiber diet leading to augmented SCFA production and supplementation has been demonstrated to be beneficial for HTN treatment. Several molecular changes associated with improved cardiovascular health and function, such as reduced SBP and DBP, cardiac fibrosis, left ventricular hypertrophy, and renal fibrosis, were induced by high consumption of fiber and supplementation with the SCFA acetate by decreasing gut dysbiosis (77). The protective effects of SCFA acetate were distinguished from the adverse effects on the microbiota, gut, brain, and BP in a model of OSA-induced gut inflammation and HTN (29).

The SCFA propionate, produced from dietary fiber, was also suggested to attenuate cardiac hypertrophy, fibrosis, vascular dysfunction, susceptibility to cardiac ventricular arrhythmias, aortic atherosclerotic lesion, systemic inflammation, and local cardiac immune cell infiltration, and thus protect from hypertensive cardiac damage and atherosclerosis (4). Other dietary interventions proposed to be effective in preventing HTN and restoring intestinal microbial changes were reported using an extra virgin olive oil-enriched diet in SHR (39).

Antihypertensive medicines that may impact BP partially through targeting GM

To date, a few known antihypertensive medicines have been identified to exert their BP regulatory role through modulating the intestinal microbiome, at least in part. Losartan is observed to restore the gut dysbiosis in F/B ratios, acetate- and lactate-producing bacteria, and strict anaerobic bacteria, and improve the gut integrity. These microbial changes after losartan treatment are supposed to contribute to vasculature protection and BP reduction (104). Lrbesartan is suggested to be beneficial for HTN treatment partially *via* preventing perturbed microbiota, with decreased abundance of *Bifidobacterium*, *Lactobacillales* spp., and *Bacteroides* corrected, and increased abundance of *Clostridium* subcluster XIVa, *Clostridium* cluster XI, and *Clostridium* cluster XVIII normalized (152).

The pharmacological role of candesartan has been shown to alleviate pathophysiological alterations in the gut, increase microbial production of SCFA, and restore gut *Lactobacillus* in the treatment of HTN (142). The antihypertensive effect of captopril has been identified to be associated with alterations in GM and improvement in gut pathology (111, 148). Evidence also suggests that modulations of GM composition participate in the preventive role of resveratrol in the development of HTN (120). Baicalin is reported to lower both SBP and DBP, and protect against HTN-associated intestinal barrier impairment in part through increasing the abundance of SCFA-producing bacteria (22, 141). Moreover, benazepril and a traditional Chinese medicinal formula of Zhengganxifeng decoction are observed to affect BP and influence gut microbial composition (153).

Potential of bacteriophage use and FMT in HTN treatment

The therapeutic use of bacteriophage to precisely modulate GM colonization and gut metabolome, and thus affect the mammalian host, is a recent and novel concept (41). Investigators have shown that phage predation shifts susceptible bacteria, leading to cascading effects on other bacterial species that have direct consequences on the gut metabolome. However,

the use of bacteriophages to prevent diseases, such as HTN, is contingent on the illumination and clarification of the specific bacterial strains that are pivotal in contributing to diseases, and also the choice of safe and targeted strains of bacteriophages.

The FMT from strictly enrolled healthy donors is another creative idea that has been considered. Although FMT has been widely accepted and used in clinical trials on patients with gastrointestinal diseases, whether it is feasible and effective for individuals with HTN remains completely unclear. Practical intervention strategies based on gut modulation to prevent HTN need further exploration (Fig. 6).

Future Prospects

Given these findings, larger numbers of fecal transplants from control participants with HTN, pre-HTN, and normotension should be conducted to examine the magnitude of changes in BP with the transfer of the gut microbiome. Current studies on GM are mostly limited to correlation. Evidence showing certain effects of specific gut strains on HTN onset is still scarce. Further, in-depth scrutiny is recommended to unveil candidate gut strains that are conducive to HTN, which can help learn about GM and develop a new treatment for HTN. Studies with mono-colonization and direct experimental testing of mechanisms showing changes in BP are encouraged. A mechanistic rationale demonstrating the function of metabolites generated by microbes and how these contribute to BP is needed.

Future studies need to advance the knowledge on GM by explaining how it impacts BP in the host by either showing causal contributions of newly defined microbial mediators or advancing the understanding of host molecular detectors

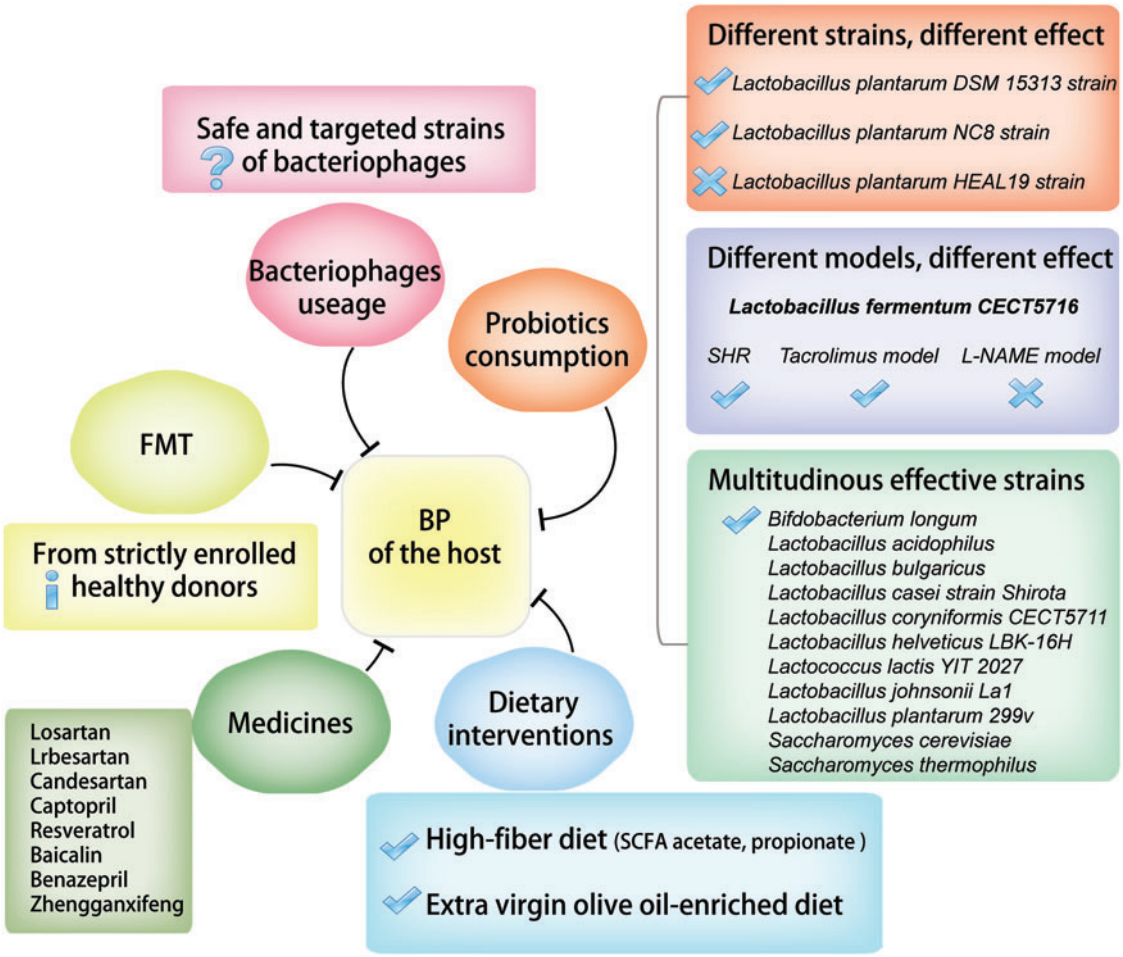


FIG. 6. Intervention strategies to correct gut dysbiosis and improve HTN development. How can we manipulate GM to prevent HTN? There are five strategies discussed in the present review, including consumption of probiotics, dietary interventions, antihypertensive medicines, bacteriophage use, and FMT. The potency for antihypertensive activity of probiotics depends on certain specific strains (shown in the *red pane*). The hypotensive effect of the same strain of probiotics varied in different models of HTN (shown in the *purple pane*). The numerous probiotics strains reported to effectively lower BP of the host are listed in the *green pane*. Using dietary interventions, high-fiber and extra virgin olive oil-enriched diets have been demonstrated to effectively lower BP of the host (shown in the *cyan pane*). A few antihypertensive medicines have been identified to exert their BP regulatory role through modulating the intestinal microbiome, at least in part. Regarding bacteriophages use, how to choose safe and targeted strains of bacteriophage is a crucial issue (shown in the *pink pane*). By FMT, one must be quite cautious to select strictly enrolled healthy donors (shown in the *yellow pane*). "✓" indicates effective. "×" indicates ineffective. "?" indicates important questions that need to be settled. "¡" indicates issues that require special attention. FMT, fecal microbiota transplantion. Color images are available online.

(*e.g.*, new metabolites, or new G-protein-coupled receptors beyond those already reported) that mediate gut microbial signaling. Functional studies should ideally show biological relevance that associates the metabolites with vascular tone, renal function, immune disorder, or other factors involved in BP control. The effectiveness of intervention strategies based on probiotics consumption, dietary interventions, bacteriophage use, and fecal transplants in preventing hypertensive disorders also needs to be explored and verified.

Conclusions

The crucial role and possible mechanisms of intestinal flora in BP regulation and HTN were discussed in this study. Further, gut flora was implicated in BP control and HTN based on the effect of antibiotics. The study discussed disordered intestinal and metabolic profiles linked to HTN, elucidated the cause–effect relationship between intestinal microbiota and BP, summarized the underlying mechanisms, and encouraged interventions targeting the gut in HTN therapy. Future directions to advance the knowledge on GM and HTN have been indicated, highlighting the significance of targeting GM in future clinical therapies to prevent the development of HTN and reduce cardiovascular risks.

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Abbreviations Used

ACE2 = angiotensin I converting enzyme (peptidyl-dipeptidase A) 2
ALDH2 = acetaldehyde-metabolizing enzyme mitochondrial aldehyde dehydrogenase
Ang II = angiotensin II
BP = blood pressure
DBP = diastolic blood pressure
F/B = Firmicutes/Bacteroidetes
FMT = fecal microbiota transplantation
FXR = farnesoid X-activated receptor
GF = germ-free
GM = gut microbiota
GPCR = G-protein-coupled receptor
Gpr41 = G-protein-coupled receptor 41
HTN = hypertension
IRGM = immunity-related GTPase M
L-NAME = *NG*-nitro-L-arginine methyl ester
NMR = nuclear magnetic resonance
Olfr78 = olfactory receptor 78
OSA = obstructive sleep apnea
OSAHS = obstructive sleep apnea–hypopnea syndrome
R = Dahl salt-resistant
S = Dahl salt-sensitive
S1PR2 = sphingosine 1-phosphate receptor 2
SBP = systolic blood pressure
SCFA = short-chain fatty acid
SHR = spontaneously hypertensive rat
SHRSP = spontaneously hypertensive rat stroke-prone
TGR5 = G-protein-coupled bile acid receptor 1
Th = T helper
Treg = regulatory T
VDR = vitamin D3 receptor
WKY = Wistar-Kyoto