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Gut microbiota-derived short chain fatty acids facilitate microbiota:host crosstalk and modulate obesity and hypertension

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Abstract

Purpose of review: The purpose of this review is to summarize the evidence supporting a role of short chain fatty acids (SCFAs) as messengers facilitating crosstalk between the host and gut microbiota and discuss the effects of altered SCFA signaling in obesity and hypertension.

Recent findings: Recent evidence suggests there to be a significant contribution of gut microbiota-derived SCFAs to microbe:host communication and host metabolism. SCFA production within the intestine modulates intestinal pH, microbial composition, and intestinal barrier integrity. SCFA signaling through host receptors, such as PPARγ and GPCRs modulate host health and disease physiology. Alterations in SCFA signaling, and downstream effects on inflammation are implicated in the development of obesity and hypertension.

Summary: SCFAs are crucial components of the holobiont relationship; in the proper environment, they support normal gut, immune, and metabolic function. Dysregulation of microbial SCFA signaling affects downstream host metabolism, with implications in obesity and hypertension.

Keywords

gut microbiome; short chain fatty acids; diet; obesity; hypertension

Introduction:

The human gut microbiome has coevolved as a vital determinant of host health, and has been linked to multiple diseases, including obesity and hypertension (HTN). Gut microbiota

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Conflict of Interest

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are indispensable to digestion and biosynthesize nutrients essential to host health. Microbiota enhance and develop the host immune response, confer resistance to infection, and are emerging as key drivers of host metabolism. Yet large gaps remain in our understanding of the bidirectional microbiota:host relationship, physiology, and related-disease etiology. The composition, health, and functionality of the gut microbiota is dependent on the host, and in return, the gut microbiota's functions as an endocrine organ can have diverse and clinically significant effects on host health. This bidirectional relationship, comprising the holobiont [1], is of great interest for its significance to human health and disease.

A consensus definition of a 'healthy' gut microbiota remains elusive due to substantial inter- and intra-individual variability, with complex interplay of the gut-host macroenvironment. Current evidence, primarily derived from observational studies, suggests that characteristics of a 'healthy' gut microbiota include greater diversity and microbial richness, greater abundance and functionality of short-chain fatty acid (SCFA)-producing bacteria, and a relatively stable-community of obligate anaerobes in larger abundance as opposed to facultative anaerobes [2–6]. Communication between microbiota and their host is facilitated by signaling messengers, such as metabolites and small molecules. The SCFAs, acetate, propionate, and butyrate, have received particular attention for their role in microbiota:host communication, with distinctive effects on both local intestinal and systemic host-physiology. Within this review we summarize the evidence supporting a role of SCFAs as messengers facilitating crosstalk between the host and gut microbiota, and discuss the effects of altered SCFA signaling on obesity and hypertension.

Host diet regulates availability of SCFA precursors and exerts selective pressure on microbial community composition

There are three primary SCFAs which have been studied for their relevance in human health: acetate, propionate, and butyrate. These are present at differing concentrations in the body, and are thought to have distinct effects on host metabolism. However, as the specific individual and combinatorial effects have not been fully elucidated, and the SCFAs are often studied together, we primarily describe mechanisms that have been attributed to SCFAs in general. The primary source of SCFAs in humans is gut microbial synthesis from dietary precursors, with some SCFAs obtained directly from dietary intake of microbial-fermented foods [7] and *de novo* synthesis by the liver or other metabolic organs [8]. Prebiotics or microbe-accessible carbohydrates, including plant-derived oligosaccharides, polysaccharides, resistant starch, and inulin, are selectively fermented by commensal SCFA-producing bacteria (Fig 1.A.a), including those within the *Clostridium* cluster IV and XIVa, and more specifically: *Clostridium Leptum, Coprococcus spp., Faecalibacterium prausnitzii, Eubacterium spp., Anaerostipes*, and *Roseburia spp* [9,10]. Some bacteria, such as those within the *Lactobacillus* and *Bifidobacteria* genus, which don't produce SCFAs themselves, contribute to the SCFA pool indirectly via metabolic cross-feeding – in which their breakdown of dietary fiber provide the necessary substrate (i.e. oligosaccharides, lactate, and acetate) for other SCFA-producing bacteria [9,11]. Diet shapes the gut microbiota by selecting for microbes which preferentially digest specific nutrients or dietary substrates. Alterations in diet can lead to rapid and significant modifications in gut microbial

composition and diversity in as little as 2–3 days [12], though these changes tend to be transient with extensive interindividual variability [13–16]. Plant-based diets, rich in complex carbohydrates, are associated with increased abundance of SCFA-producing bacteria [17–20], while greater intake of saturated fat, animal products, and simple sugars associates with an increase in facultative anaerobic bacteria and diminished SCFA abundance due to both a reduction in SCFA-producing bacteria and enhanced excretion of SCFAs (Fig 1.B.a) [2,12,21–25]. Interestingly, although very-low-carbohydrate diets may reduce SCFA-substrate availability, they may contribute to the SCFA-pool and mimic SCFA-functionality by increasing production of ketones, which can be utilized as a fuel source for colonic epithelial cells (CECs) and participate in similar signaling pathways [26]. However, diet alone is not a consistent predictor of SCFA production or abundance. The considerable interindividual variability observed in the response to dietary interventions may be due to differences in gut microbial composition. Individuals with lower microbial richness and diversity are shown to have a more robust response to a variety of interventions [16,27,28]. Still, some evidence suggests variability in the change in bacterial composition and metabolite production in response to dietary intervention, regardless of baseline microbial richness and diversity [28–30]. Whether this is related to host genetics, or other factors, is unknown, and more research is needed to define the determinants of response to dietary interventions. However, baseline gut microbial composition has been successfully used to predict a subject's response to an intervention, establishing feasibility for precision nutrition approaches aimed at altering SCFA production [31–36••].

SCFAs are metabolically active, and interact with host signaling at local and systemic levels

SCFAs are key players in the holobiont relationship. Their production, absorption, and distribution into systemic circulation are critical determinants of their functionality as secondary messengers. They are primarily produced in the cecum and ascending colon where they alter gut pH, indirectly regulate gastrointestinal (GI)-motility and blood flow, influence nutrient bioavailability, foster normal immune-function, and promote GI-health and stability [37,38]. SCFAs not utilized for fuel by colonocytes or metabolized by other microbes are either absorbed or excreted. Due to their relatively short-carbon-chain length (less than 6-carbons), both dietary and gut microbiota derived SCFA do not require micellarization to be absorbed nor re-esterification once inside cells [39]. Absorption occurs through several mechanisms within the colon depending on the SCFA-hydronation state. Protonated-SCFA are absorbed in the colon-epithelium via simple diffusion down a chemical gradient; whereas nonionic forms operate under carrier-mediated transport [40]. These transporters include monocarboxylate transporters (MCT1 and MCT4) which require an ancillary chaperone protein, CD147, for translocation to the cell-surface, and sodium-coupled-MCTs (SMCT1 and SMCT2) (Fig 1.A.b) [40]. MCT1, SMCT1, and SMCT2 transporters are expressed on the apical membranes of intestinal epithelium, whereas, MCT1 and MCT4 are expressed basolaterally (Fig 1.A.b) [40]. Transporter expression is regulated by SCFAs and by inflammation, and SCFA uptake may be altered in the setting of obesity and certain disease states [6,41–43].

After absorption, SCFAs are taken up directly into the portal vein en route to the liver, where they can be used as an energy source, incorporated into endogenous molecules (i.e. cholesterol, fatty acids, glucose), or function as signaling molecules (Fig 1.A.h) [44]. Excretion of remaining SCFA from the body occurs in the stool, urine, and breath [44]. As a consequence of rapid and efficient splanich-extraction, relatively little SCFAs make it into circulation [44–46], which is especially the case for butyrate. After meeting approximately 70–90% of the CECs' energy needs, filtration of butyrate by the liver is upwards of 100%, with little reaching systemic circulation [44–46]. In spite of this, circulating SCFAs are still shown to play some role in cardiometabolic health [47], suggesting concentration- and receptor-dependent effects. Furthermore, evidence suggests differential effects of individual SCFAs, with potentially opposing or synergistic activity [48]. Additional studies are needed to better clarify this relationship.

SCFAs modulate gut barrier health

Butyrate has beneficial effects on various organ-systems, including the brain, skin, immune system, and most notably, the GI-tract. Within the gut, butyrate exerts beneficial effects by suppressing colonic inflammation, regulating cell cycle, and improving gut-barrier integrity (Fig 1.A.) [9]. The structural integrity of the gut and the mucus layers which protect it are paramount for maintaining symbiotic homeostasis. Butyrate boosts mucus production via epigenetic regulation of mucin (Muc2) expression in goblet cells by either promoting histone acetyl transferase (HAT) activity at low concentrations or inhibiting histone deacetylase (HDAC) activity at higher concentrations (Fig 1.A.g) [49,50]. Enhanced mucus-production within the dense inner-layer along the apical membrane of CECs protects the gut-lining from infiltration and exposure to both pathogen and commensal bacteria alike, tamping down the innate immune response, and reducing overall inflammatory-tone [15]. Enhanced production of mucus within the 'outer-layer' provides bacteria with a semi-stable home and for some, a glycoprotein substrate for fermentation [51]. The reduction of luminal pH as a byproduct of dietary-fiber fermentation and commensal SCFA production adds an additional layer of protection from pathogenic bacterial infiltration and colonization [52].

Host G-protein coupled receptors mediate SCFA secondary signaling actions

SCFAs are potent signaling molecules which bind to G-protein coupled receptors (GPCRs), including Gpr41 (FFAR3), Gpr43 (FFAR2), Olf78 (OR51E2), Gpr91, Gpr109A (HCAR2), and Gpr164 [53–55]. The GPCRs are widely expressed in many cell- and tissue-types and demonstrate varying affinity for SCFA-ligand activity [54]. Through HDAC regulation and GPCR signaling, SCFAs stimulate the production of anti-inflammatory mediators, enhance the differentiation and activation of regulatory T-cells in both the intestines and peripheral organs, and can attenuate the migration and subsequent inflammatory response in macrophages and neutrophils (Fig 1.A.f) [56]. Interestingly, this pathway may have multi-generational effects on metabolic disease. Gut microbiota-derived SCFAs cross the placental-barrier during pregnancy, and modulate metabolic and sensory neural development in murine offspring via Gpr43 and Gpr41, respectively [57••]. This represents an additional "hidden" mechanism whereby gut microbial SCFA signaling modulates disease risk and may confound our ability to identify consistent and reproducible associations between gut microbiota and hosts within a single generation.

Butyrate - PPARγ signaling maintains healthy intestinal function

In the healthy gut, butyrate and to a lesser extent propionate and acetate, act as ligands which bind to and selectively activate peroxisome proliferator-activated receptor gamma (PPARγ) [58,59]. This signaling in mature CECs transcriptionally regulates and activates mitochondrial β-oxidation (Fig 1.A.d) [59]. Metabolism of both short- and long-chain fatty acids enhances oxygen consumption via oxidative phosphorylation. The subsequent reduction of oxygen available to freely diffuse across epithelial membranes procures an optimal partial pressure of <1% oxygen, maintaining physiological hypoxia [60]. Additionally, butyrate-mediated oxygen-depletion in CECs helps to stabilize hypoxia-inducible factor 1 (HIF1) which in turn upregulates expression of genes critical to gut-barrier function, such as occludin, zonula occludens, and junctional adhesion molecules (Fig 1.A.e) [61,62].

Conversely, reduced abundance and bioavailability of butyrate may be a common link in many of the disorders of the gut and creates a vicious feed-forward cycle. Whereas normal PPARγ-butyrate signaling would downregulate production of pro-inflammatory cytokines via inhibition of the nuclear factor-κB pathway (Fig 1.A.f), diminished production or impaired uptake of butyrate and inadequate expression or activation of PPARγ induces inflammation (Fig 1.B.f) [63–65]. Inflammation and lack of microbially-derived substrate drives metabolic reprogramming in CECs, forcing them to pull glucose from the bloodstream as their primary fuel source, utilizing glycolysis in lieu of fatty acid β-oxidation (Fig 1.B.d) [38]. This switch to anaerobic respiration significantly reduces oxygen consumption, prompting loss of luminal hypoxia and creating a selective advantage for pathogenic facultative anaerobes, such as Proteobacteria [38]. Within the Proteobacteria phylum, the *Enterobacteriaceae* are a family of rapidly dividing, aerotolerant, and simple-sugar-oxidizing bacteria including several notorious pathogens, such as *E. Coli, Salmonella, Enterobacter, Shigella*, and *Yersinia*, of which are well documented to induce pro-inflammatory responses and are now considered to be a signature of gut microbiota dysbiosis [24,64,66]. Left unchecked, these pathogens will exhaust exogenous-nutrient availability and turn to metabolizing, and therefore diminishing, the protective mucus layers. This allows bacterial interaction with the mucosal barrier, inciting immune-cell activation and pro-inflammatory cytokine release (Fig 1.B.e–f). Ultimately, this impairs gut-barrier integrity allowing leakage of luminal contents into systemic circulation – further exacerbating inflammatory conditions and inducing metabolic endotoxemia (Fig 1.B.f, h) [67].

The inflammatory cascade resulting from direct exposure of bacteria to the mucosa or intestinal damage stimulates colonic-crypt stem cell proliferation [68]. However, butyrate deficiency impairs PPARγ-mediated growth and differentiation; therefore, these transitionally suspended cells ascend from the crypts to the luminal surface without fully developing into mature colonocytes or goblet cells [38,61].This cell-developmental stunting results in reduced PPARγ expression and impaired cellular-functionality in colonocytes as well as reduced mucus production by goblet cells – initiating a positive feedback loop for further detrimental effects (Fig 1.B.c–g). PPARγ is also a critical mediator of the host-innate immune system within the colon, maintaining expression of the major microbial ‘defense’

system, β-defensin [69], and preventing diminution of the anti-inflammatory immunoglobulin A in response to acute stress (Fig 1.A.f) [70]. Therefore, activation of PPARγ is required to activate aerobic metabolism and maintain luminal hypoxia, properly differentiate CECs, and to support immune system and gut-barrier function.

Microbial-derived SCFAs are an important energy source, with relevance for energy homeostasis and obesity

The gut microbiome in the obese state is typically characterized by inflammation, dysbiosis, and in many reports, a relative increase in Firmicutes to Bacteroidetes [71–75]. However, data regarding the Firmicutes to Bacteroidetes ratio are inconsistent, and measurement at the phylum level likely vastly over-simplifies the relationship, given the huge variability in function at the species and strain level [76,77]. Evidence is currently lacking in humans to determine whether this ratio is a driving force for obesity, a reflection of host genetics or diet, or caused by disease itself [15]. In support of a causal role for gut microbiota in obesity, germ-free mice tend to gain less weight than wild-type mice on the same diet [78], possibly from the reduced production of SCFAs, while fecal material transfer (FMT) from obese mice and humans result in significant weight gain [3,78,79]. Furthermore, obesity-related alterations in the gut microbial composition has been implicated in contributing to weight regain greater than baseline during yoyo dieting [35]. SCFAs have significant local and systemic effects on host metabolism, energetics, and appetite control, making them a compelling factor in the study of obesity pathophysiology [80]. Gut microbiota derived SCFAs are primarily used to meet the energy needs of cells lining the mucosa and provide an additional source of calories to the host. The ‘in vs out’ theory of energy flux is thus an overly simplified model which disregards the metabolic complexities of the holobiont [81]. Unlike closed thermodynamic systems, humans are complex and dynamic metabolic systems, where gut microbiota contribute up to 10% of the host’s total daily energy needs with variable energy extracting efficiency [3]. Whether this enhanced harvesting is a function of gut microbiota composition independent of energy intake, or if composition changes occur to compensate for excessive energy intake requires further examination.

Beyond providing energy directly, SCFAs stimulate enteroendocrine L-cells to produce satiety hormones such as peptide YY (PYY) and glucagon-like peptide (GLP-1) locally (Fig 1.A.c), while in circulation they epigenetically regulate expression of adipokines such as leptin, adiponectin, and resistin (Fig 1.A.h) [82–86]. In addition, SCFAs may indirectly contribute to obesity through modulation of intestinal and systemic inflammation, promoting or exacerbating cardiometabolic dysfunction (Fig 1.A.h & 1.B.h) [15]. Obese individuals have been reported to have a greater abundance of fecal-SCFAs, yet relatively low plasma-SCFA levels (Fig 1.B.h) [3,6,87,88]. This may suggest defects in absorption into the colonocyte and systemic circulation [47]. Alteration of epithelial cell gene expression networks within the gut coordinating nutrient metabolism and inflammation, as well as SCFA and cytokine-mediated downregulation of SCFA-transporters may at least partially explain the reduced uptake and increased fecal excretion (Fig 1.B.b) [43,63]. Thus, in the setting of inflammation and obesity, SCFAs produced in the intestine may be less able to mediate their systemic-second messenger effects. Interestingly, several human clinical trials demonstrated SCFA-supplementation to enhance resting and total energy expenditure as

well as augment fat-oxidation (Fig 1.A.h) [89,90]. Although administration location and method or SCFA type may have differential effects on metabolic outcome, most studies demonstrate beneficial effects of SCFAs in human obesity studies [89–92]. Taken together, these data suggest that SCFAs may modulate the development of obesity via caloric availability and appetite regulation; however, there may be paradoxical effects in the setting of established obesity. The increased fecal levels of gut microbiota-derived SCFAs in obese individuals may reflect overall greater substrate availability, reduced absorptive capacity, or a state of "SCFA-resistance". Further studies are needed to resolve these questions.

The unique interplay of the gut microbiota and hypertension

The GI-tract is the gatekeeper for many of the primary modifiable risk factors contributing to HTN, including an excess intake of sodium, alcohol, lipids, and simple carbohydrates. Conversely, fiber is a well-known cardioprotective-agent shown to lower arterial blood pressure [93], which also has direct interaction with the GI-tract. These interactions provide a compelling link, bridging the effects of the gut microbiota and HTN. As with several other diseases, the mechanisms linking the gut microbiota to HTN include dysbiosis, inflammation, intestinal permeability, and reduced production of SCFAs, especially butyrate [94–96]. A recent large multi-ethnic cohort describes an association of altered gut microbial composition and blood pressure while demonstrating large discrepancies among different ethnic groups [97••]. Studies using metabolomic and metagenomic sequencing of stool samples from either prehypertensive or hypertensive subjects observed diminished microbial diversity and richness, reduced butyrate producers and abundance, and prominent intestinal inflammation and permeability versus their normotensive counterparts [94–96]. Similar observations were recently made in pregnant women diagnosed with preeclampsia [98•]. Broad-spectrum antibiotic use is also implicated in contributing to gut dysbiosis and either directly causing or exacerbating the hypertensive response, possibly in an individual or genetic-dependent manner [99,100]. The SCFA-paradox seen in obesity is recapitulated in recent HTN-studies. SCFA-producing bacteria and plasma-SCFA levels were inversely proportional to blood pressure while fecal SCFA content was positively associated with blood pressure [97, 101••]. Furthermore, mice humanized with stool samples from hypertensive-subjects displayed donor-symptomology, establishing a gut microbiota-transferrable augmentation in blood pressure, and a possible direct effect in this model [95]. Similar studies conducted in rodent-analogous models obtained comparable results [102–105].

The intestinal microbiome was recently demonstrated to play a role in circadian rhythm coordination of water retention and diurnal variation in blood pressure [106,107]. Temporal dynamics and sympathetic nervous system activity of the gut microbiota and its metabolites have also been implicated in obstructive sleep apnea-induced HTN [102,106–110]. This was primarily contributed to gut dysbiosis, inflammation, and permeability [102,106–110] and can be exacerbated by excessive dietary salt intake (Fig 1.B.h) [107,109]. In some cases, commensal gut bacteria-derived peptides confer anti-inflammatory benefits while also modulating host hypertensive hormones, such as angiotensin converting enzyme and renin [111]. The neuro-gut-immune axis and its interactions with hormone-related compounds in regards to blood pressure regulation has been recently reviewed [112].

SCFAs have therapeutic potential for hypertension

Normal production and function of SCFAs have been considered beneficial in most diseases, including HTN. SCFAs signal through GPCRs in the kidney, heart, gut, immune cells, and vasculature to modulate blood pressure primarily through regulation of vascular tone and inflammation (Fig 1.A.h) [113–115]. Biologically, this mechanism may be used to enhance blood flow and exchange of nutrients after digestion and absorption; however, this has alternatively elicited advantageous effects on blood pressure regulation [116]. Prebiotic and probiotic supplementation associated with enhanced SCFA-production reduce blood pressure in both genetic and diet-induced HTN experimental models [110,117–119]. Manipulation of SCFA abundance, production, and function either via modulation of the gut microbiota through dietary supplementation with prebiotics, targeted microbiota therapy with antibiotics and probiotics, or via direct supplementation with SCFA are promising strategies still requiring further study. Experimentally, supplementation with SCFA was shown to reduce blood pressure, as demonstrated by using specialized oral formulations [94,98,115,117,120,121], as well as intraperitoneal [94] and intragastric infusions [110]. The composition of SCFA oral supplementation for therapeutic use must be carefully considered; controlled-release systems such as pH-sensitive polymers or coatings, time-release capsules, or covalent connections with colonic bacterial-degrading compounds are required to promote bioactive signaling and avoid utilization by the host as energy substrates in the proximal small intestine [44]. While additional experimental studies and well-designed clinical trials are required to obtain a better understanding of SCFA-kinetics in health and disease states, SCFAs remain a promising target for future management of hypertension and inflammatory cardiometabolic disease.

Bridging the Gap:

The bidirectional relationship of the gut microbiota and human health is still a nascent area of research with many questions that remain to be addressed. Although relatively well studied, much of the individual SCFAs direct, opposing, synergistic, and off-target effects in humans remain largely unknown. Discrepancies in SCFA quantification methodologies, as well as large interindividual variation, exacerbate difficulties in cross-study comparability. Due to the low relative concentrations and dynamic nature of SCFAs in circulation, it remains unclear whether measurement of SCFAs in serum or plasma, as is commonly implemented in epidemiological studies, is informative for health status. Fecal or tissue measurements may be required to better understand the physiological effects of SCFAs in clinical and population studies, but these introduce logistical challenges. Rigorous and standardized methodologies are needed to better assess dietary intake, define microbiome composition, and quantify individual SCFAs at relevant sites of action. Multidisciplinary collaborative approaches may be needed to better understand and predict gut microbiota functionality, and move towards mechanistic understanding [122].

Conclusions:

In conclusion, SCFAs are bioactive microbiota-derived signaling molecules, which play diverse roles in human health, and represent a key mechanism whereby microbiota

communicate with their hosts. Understanding the mechanisms of SCFA signaling, and their association with obesity, hypertension and cardiometabolic disease risk is an active research area, which promises to shed light on disease pathophysiology and may open new therapeutic avenues for disease prevention and treatment.

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•• Of major importance

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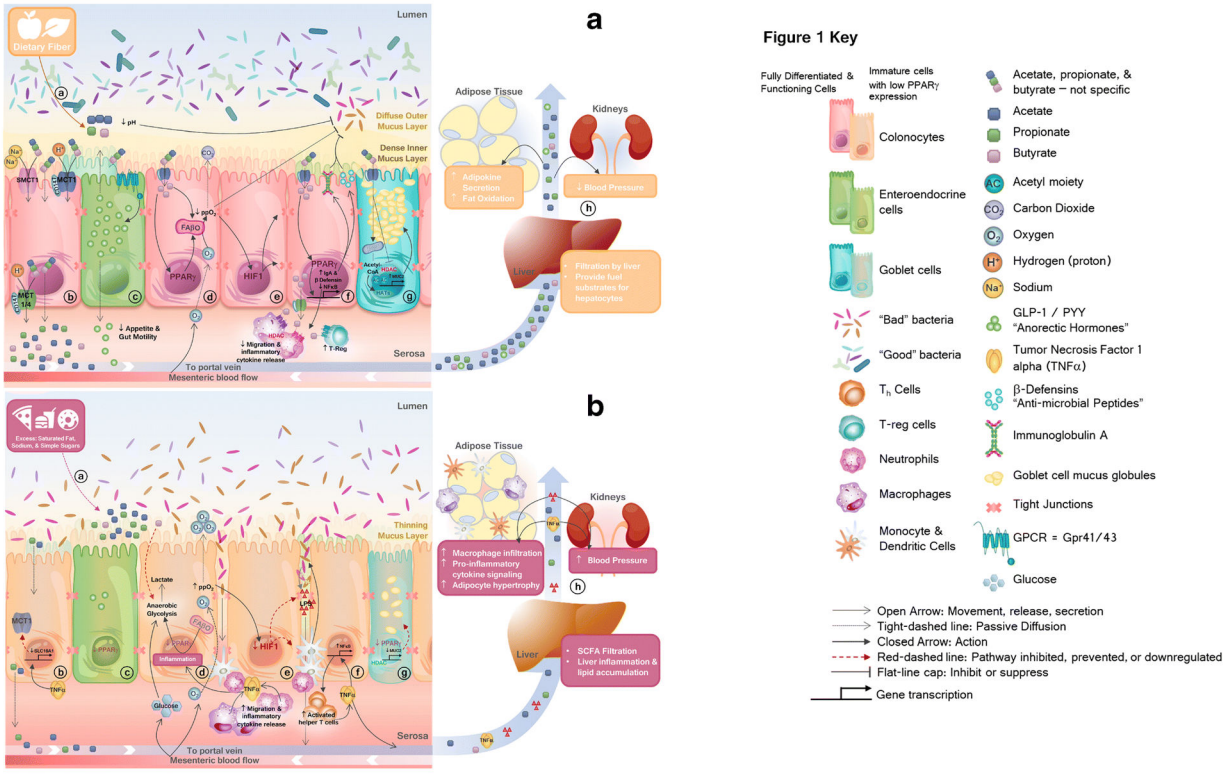

FIGURE 1. Gut microbiota-derived short chain fatty acids modulate host health with implications in obesity and hypertension

A.

a) Dietary fibers provide substrate for commensal bacteria to produce short chain fatty acids (SCFAs), acetate, propionate, and butyrate. Bacterial fermentation of dietary fibers reduces luminal pH. b) Protonated-SCFAs can passively diffuse through the membrane, while anionic-SCFAs require carrier mediated transport (by MCT1, MCT4, SMCT1 and SMCT2) c) SCFAs bind to and activate Gpr41/43, causing secretion of anorectic hormones, peptide YY (PYY) and glucagon-like peptide (GLP)-1, d) Within fully differentiated colonocytes, SCFAs activate peroxisome proliferator activated receptor gamma (PPARγ) which activates mitochondrial fatty acid beta-oxidation (FAβO), reducing luminal availability of oxygen. e) Within colonocytes, hypoxic conditions activate hypoxia-inducible factor 1 (HIF1), which upregulates expression and function of tight junction proteins, maintaining gut barrier integrity. f) Butyrate activation of PPARγ upregulates anti-inflammatory immunoglobulin A (IgA) and beta-defensin (β-defensin) expression and inhibits nuclear factor kappa b (NFκB) signaling. Butyrate enhances activation of regulatory T-cells and suppresses migration, activation, or release of pro-inflammatory mediators from resident immune cells via histone deacetylase (HDAC) inhibition and GPCR-signaling. g) Fully differentiated and functional goblet cells with sufficient PPARγ expression allows butyrate-mediated histone acetyltransferase (HAT) or HDAC-inhibition-mediated upregulation of mucin, or MUC2, maintaining a healthy mucus layer. h) SCFAs which are not used in colonocyte metabolic processes, are sent to the periphery via portal circulation where they elicit beneficial systemic effects.

B.

a) Excess dietary saturated fat, sodium, and simple sugars provide nutrient advantage for facultative anaerobic bacteria. b) Inflammation downregulates SCFA-transporters, reducing colonocyte uptake and systemic circulation of SCFA. c) Reduced SCFA signaling and activation of PPARγ within intestinal crypts dysregulates normal growth and proper differentiation of cells. d) Diminished abundance and uptake of SCFAs limit substrate available to fuel colonocytes, and may prompt a metabolic switch from high oxygen-consuming mitochondrial FAβO to anaerobic glycolysis, forcing cells to pull exogenous carbon-sources from blood-supply (i.e. glucose) resulting in lactate production. e) Loss of cellular and luminal physiological hypoxia reduces HIF1 expression, resulting in loss of tight junction and adhesion molecule expression and function. This allows bacterial translocation, triggering the innate immune response. f) Release of endotoxin lipopolysaccharide (LPS) induces pro-inflammatory NFκB signaling. g) Immature goblet cells lacking proper PPARγ and SCFA-signaling produce less mucin, leading to a reduced mucus layer. Nutrient selection, reduced bacterial competition, and increased luminal oxygen availability provide a selective advantage for pathogenic overgrowth. h) Local intestinal inflammation leads to organ-specific and systemic inflammation, increasing cardiometabolic risk.