

Gut Microbiome Metabolites and the Intestinal Homeostasis

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Abstract

Gut microbiota, the collection of microorganisms harboring the gut of all mammals, are essential for the host's physiology, metabolism, intestinal homeostasis and immune system development and function. The advancement of technology has allowed a better understanding of the gut microbial communities and their metabolites, how they influence the host's physiology and homeostasis, and how they also influence the susceptibility of the host to many diseases and disorders. In this mini - review, we will focus on discussing the influence of gut microbiota-derived metabolites on intestinal homeostasis by balancing gut microbiome composition, epithelial barrier integrity and immune activation.

Keywords: gut microbiota; intestinal homeostasis; metabolites

Introduction

The mammalian intestine harbors a diverse and active community of trillions of microorganisms [1]. The dynamic host-microbiota interaction is important for the host's physiology and homeostasis. Maintaining mutualistic symbiotic host-microbiome relationship allows the host to adapt diverse saccharolytic enzymes that complement the limited saccharolytic diversity encoded in the mammalian genome [2]. Coordinated crosstalk among microbiota, and the host's intestinal epithelial and immune cells ensure intestinal homeostasis and avoid aberrant immune activation [3,4]. Perturbation of the symbiotic host-microbiome interaction leads to dysbiosis -an imbalance of the composition or function of microbiome-, which is associated with inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) [5,6]. Recent genome-wide association studies and animal models suggest that dysfunction of tight junctions (TJ) in the intestine is associated with the pathogenesis of IBD [5,7]. Moreover, dysbiosis is associated with alterations in allergies [8], metabolic disorders [9], and immune-related diseases [10].

Dysbiosis is caused by environmental factors such as a changes of the diet and antibiotics that may destroy the epithelial barrier function and initiate a proinflammatory response [11]. The gut microbiome is crucial for the metabolism of diverse dietary compounds to produce active metabolites that provide information to the host about the microbiome composition, the existence of pathogens, or other environmental stress (12). With the advancement of metabolomics analysis technologies, it has become available to observe changes of different types of metabolites in IBD patients in comparison with healthy subjects, such as bile acids, medium-

and short- chain fatty acids, and polyamines [13]. Numerous studies have reported that the impact of the gut microbe metabolites on gut barrier function [14]. Besides, there are clinical trials microbiome bioactive metabolites to restore the healthy intestinal barrier function in IBD patients [15–17].

In this mini - review, we will discuss how the intestinal microbiota metabolites regulate gut barrier function, epithelial proliferation, balanced gut microbiota composition, and intestinal immune activation.

Short-chain fatty acids

The human diet is rich in dietary fiber and indigestible carbohydrates that cannot be digested in the proximal digestive system. Instead, they are fermented by gut commensals, including *Bifidobacterium*, *Bacteroides*, *Enterobacter*, *Faecalibacterium*, and *Roseburia* species, which produce short-chain fatty acids (SCFAs) as a byproduct [18]. SCFAs mainly comprise acetate, propionate and butyrate [19,20]. SCFAs impact gut microbiota composition and the host's metabolism and immune responses (21). Abberant levels of SCFAs are linked to disease development such as diabetes, obesity, and colorectal cancer [22].

SCFAs boost TJ protein expression, paracellular transport, zonula occludens (ZO)-1 and occludin (OCLN) maintenance, inhibit NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, and enhance autophagy [23]. In addition, high concentrations of SCFA enhances anion release, which maintains gut microbiome symbiosis [24,25]. Diets rich in SCFAs promote colonic mucin-2 (MUC2) and

OCN expression, enhancing gut barrier function, and butyrate may reduce inflammation-induced barrier disruption [26,27]. Furthermore, SCFAs regulate intestinal barrier by stimulating the secretion of antimicrobial peptides and secretory immunoglobulin A (sIgA), which prevent the adherence and invasion of harmful bacteria [28]. Butyrate serves as the primary energy source for colonocytes [29], with human colonocytes from different regions utilizing over 70% of oxygen through butyrate oxidation [30]. Patients with IBD exhibit dysbiosis and reduced levels of SCFAs/butyrate-producing bacteria [21].

Bile acids

Bile acids (BAs) are synthesized in its primary form by pericentral hepatocytes, followed by their transfer to the gut via enterohepatic circulation [31]. The conversion of primary BAs into their secondary form is executed by the gut microbiota such as *Bifidobacterium*, *Bacteroides*, *Clostridium*, *Lactobacillus*, *Enterobacter* [32,33]. In humans, primary bile acids include cholic acid (CA) and chenodeoxycholic acid (CDCA) converted into secondary bile acids such as deoxycholic acid (DCA), ursolic acid, ursodeoxycholic acid (UDCA), and lithocholic acid (LCA). In mice the primary bile acids are cholic acid, CDCA, 6-hydroxylated bile acids, and muricholic acid, which further converted into the secondary bile acids DCA, ursolic acid, UDCA, murideoxycholic acid, and hydoxycholic acid [34].

Secondary BAs exert multiple biological functions on the intestine via binding to the nuclear membrane farnesoid X receptor (FXR) and the G protein-coupled receptor; Takeda G protein-coupled receptor 5 (TGR5) in the intestines [35]. In human epithelial cell line, Caco-2, modification of the composition of BAs alters the permeability of the intestinal mucosa and impact the function of the barrier by regulating the expression of tight junction proteins [36]. For example, mice undertaken high fat in their diet have an increase in DCA, which is a major risk factor enhancing colorectal cancer [37]. UDCA supplementation has been shown to attenuate inflammation and reduce intestinal permeability caused by multidrug-resistant extended-spectrum β -lactamase (ESBL)-producing *E. coli* in colibacillus diarrhea of newborn dairy calves [38].

Furthermore, BAs modulate immune responses in the intestine [39]. Two derivatives of LCA, 3-oxoLCA and isoalloLCA, suppress T helper 17 (Th17) cell differentiation and increased the differentiation of Treg cells through the production of mitochondrial reactive oxygen species [40]. In addition, BAs impact the function of macrophages and affect the homeostasis of the intestinal immune barrier. High-fat diet impacts bile acids (e.g., increased CA and DCA), gut microbiota composition, pro-inflammatory macrophage polarization, which subsequently leads to intestinal inflammation [41,42].

Polyamines

Polyamines regulate multiple cellular functions including cell development, amino acid and protein synthesis, oxidative DNA damage, proliferation and differentiation [43]. The natural polyamines, including spermidine, spermine, and their precursor putrescine are important for the host's physiology, mainly for intestinal maturation and the differentiation and development of immune system [33,44,45]. Gut microbes such as *E. coli*, *Bacteroides* spp. and *Fusobacterium* spp. can synthesize polyamines [46]. Multiple studies have shown that polyamines are essential for maintaining the intestinal barrier through enhancing the expression of TJs and adherens junctions (AJs) [47–50]. Additionally, polyamines suppress gut mucosal inflammation by inhibiting inflammatory cytokine synthesis in macrophages [51,52].

Tryptophan and indole derivatives

Gut microbiota such as *Clostridium* spp., *Bacteroides* spp. and *Escherichia coli* metabolize dietary tryptophan into indole and indole derivatives (53). Indole derivatives include indole acrylic acid, indole-3-aldehyde, indole-3-propionic acid, indole-3-acetic acid, and indole-3-acetaldehyde. Tryptophan metabolites function as bacterial quorum sensors to communicate with bacteria and their host. Besides, tryptophan metabolites mediate the host's intracellular signaling via binding to aryl hydrocarbon receptor (AhR), pregnane X receptor and retinoid-related orphan receptor gamma-t [54,55].

Tryptophan metabolites' signaling through AHR impact on the intestinal homeostasis by modulating immune responses through acting on Th17 cells, macrophages, dendritic cells, and neutrophils and also decrease the pathogen colonization [56,57]. AhR signaling, primarily on immune cells, promotes the expression of interleukin-22 (IL-22), which maintains gut barrier integrity through promoting mucosal wound-healing and the expression of antimicrobial peptides (AMPs) by intestinal epithelial cells [57].

Choline metabolites

Trimethylamine (TMA) is a byproduct generated by the gut microbiota, such as *Bifidobacterium*, Firmicutes, Proteobacteria, Actinobacteria, *Faecalibacterium prausnitzii* from dietary amines such as choline, betaine, and carnitine that originate from animal-based foods by the action of hepatic flavin-containing monooxygenases (FMOs) such as FMO1 and FMO3 [33,58,59]. TMA is absorbed into the portal circulation and is oxidized by the liver into trimethylamine-N-oxide (TMAO) [59,60]. TMAO has been shown to display pro-inflammatory, pro-atherogenic, and pro-thrombotic properties [61–65]. For example, it was reported that increased levels of TMAO promote oxidative stress and inflammation of endothelial cells, activate the inflammasome and inflammatory signaling in vascular smooth muscle cells, promote the transformation of macrophages into foam cells, promotes platelet hyperreactivity, and alters cholesterol transport and bile acid synthesis [66]. TMAO may promote the pathogenesis of IBD by impacting autophagy and activating NLRP3 inflammasome [67].

Polyphenolic derivatives

Dietary polyphenols are metabolized by the gut microbiota such as *Bifidobacterium*, *Lactobacillus*, *C. difficile*, *F. prausnitzii*, to bioactive metabolites including urolithins (Uro A,B,C,D, and iso-urolithin A) [33,68,69]. UroA enhances gut barrier integrity through upregulation of TJ proteins [70]. Treatment with UroA alleviates colitis in mice through enhancing gut barrier function and suppressing the production of pro-inflammatory cytokines [70].

Conclusion and future perspectives

The current mini review postulates a summary about the role of gut microbiome metabolites in the maintenance of the intestinal homeostasis through regulating the intestinal epithelial integrity, gut microbiota composition, epithelial proliferation, and intestinal immune homeostasis (Figure. 1). Metagenomic research on gut microbiota from IBD patients have revealed that gut microbiota actively interacts with IECs for the regulation of barrier integrity. Moreover, IBD patients is characterized by gut dysbiosis, which is associated with impaired intestinal barrier and aberrant immune activation. Better understanding of host-gut microbiome interaction will eventually become a valuable tool for harnessing the power of microbial metabolites to restore gut barrier integrity, and can reveal advanced therapeutics not only for intestinal inflammation, but also for other immune- and metabolic-related disorders.

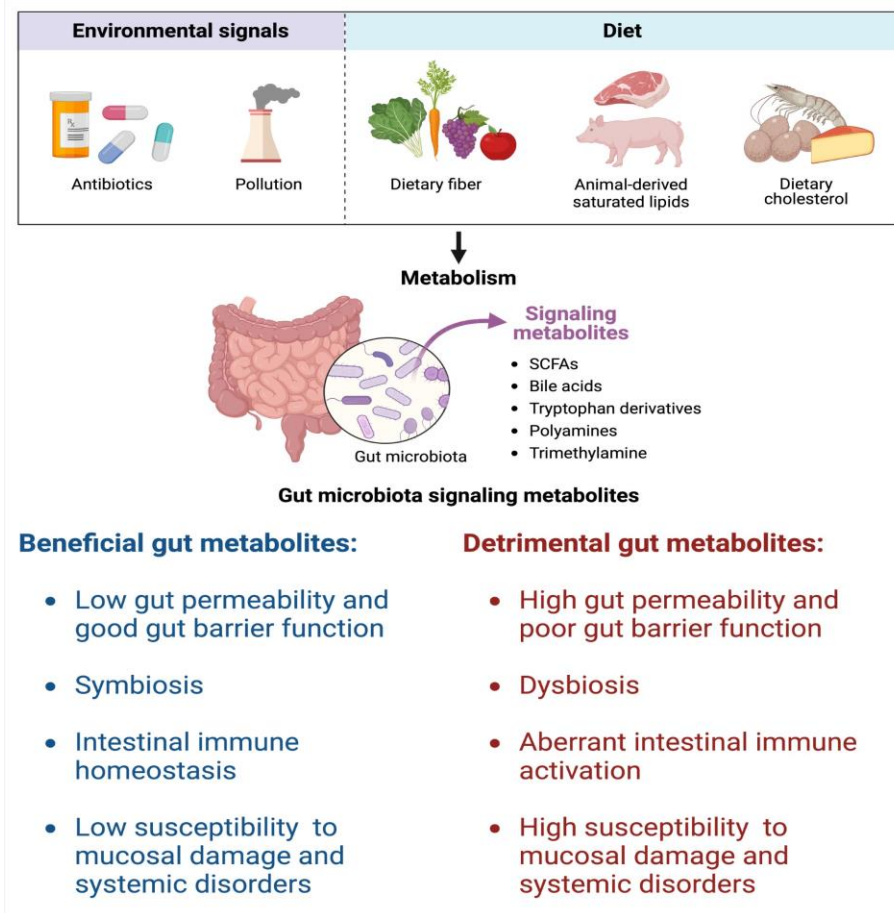


Figure 1. The role of gut microbiota metabolites in the regulation of intestinal homeostasis. Please explain the figure in the legend.

Environmental factors such as antibiotics and changes of the diet affect the balance of gut microbiota metabolites. Effects of beneficial (left) and detrimental (right) gut microbiota metabolites on intestinal homeostasis and inflammation.

Author Contributions

M.M.E wrote the manuscript draft. H.M. and T.K edited the manuscript and supervised the work.

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