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Microbiome control of innate reactivity

Feidi Chen and Thaddeus S Stappenbeck

Numerous scientific disciplines, including immunology, are now positioned to fully realize the potential of the intestinal microbiome to modulate a wide array of basic processes. Increasingly, microbiota-derived metabolites are being recognized for mediating these effects. Coupled with advances in large scale sequencing and mass spectrometry, research into the microbiota and their metabolites has entered into an era of rapid discovery. Here, we review recent studies that have shown how-specific metabolic products of the microbiome alter properties of the innate immune system that in turn modulate response to infection and immunity.

Address
Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

Corresponding author: Chen, Feidi (stappenb@wustl.edu)

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Microbiome and the innate immune system

The human intestine harbors a complex community of microbes known collectively as the gut microbiome. This community can influence nearly every aspect of host physiology from development to metabolism, immunity, and behavior [1]. Large scale projects such as the Human Microbiome Project and the Metagenomics of the Human Intestinal Tract (MetaHIT) have led the way to define the dynamic composition of microbiome and their metabolic products in a variety of disease states. The major challenge is now to understand the mechanisms by which the microbiome impacts host physiology. The innate immune system is a particularly interesting and important target for the study of the effects of select microbes and their products as there are numerous experimental readouts that can be utilized during infection and control of inflammation. Metabolites are produced by the microbiome from dietary components, host products, or other microbial metabolites. These metabolites have provided interesting substrates to elevate our understanding host–microbial interactions in this area [2].

Preserving the symbiotic relationship between host and microbiome requires a constant immune surveillance system and barrier formation. As the front line of host defense, innate immunity plays a key role in recognition of and response to microbial-derived products and the production of cytokines, antimicrobial proteins, and a physio-chemical barrier. Innate immunity begins with a single layer of intestinal epithelial cells (IECs) and their products which forms not only a physical cellular barrier to luminal microbes but also a chemical barrier composed of mucus, produced by goblet cells and antimicrobial proteins, produced by Paneth cells. IECs are directly exposed to luminal contents and express pattern recognition receptors (PRRs) and G protein-coupled receptors (GPCRs) to sense microbial products. These cells serve as gatekeepers for the availability of microbial stimulation which regulates the activity of traditional innate immune cells such as macrophages and innate lymphoid cells [3].

How microbiome-derived metabolites orchestrate intestinal homeostasis by mediating cross-talk between the microbiome and the host immune system has recently drawn great attention. Aberrant changes in microbial metabolites and modulation of host innate immune response are correlated with diseases such as inflammatory bowel disease [4–6], metabolic diseases [7,8] and infection [9,10•]. In this review, we focus on recent progress in defining the innate immune responses by microbial metabolites.

Experimental *in vivo* tools to test the roles of select microbes include the use of gnotobiotic mice, with or without the addition of a defined microbiome, and antibiotic treated conventionally raised mice that eliminate select populations of microbes. These methods provided a basis to study the physiological function of components of the microbiome. For microbial metabolite studies, both gnotobiotic and broad spectrum antibiotic-treated mice contain diminished levels of certain microbial metabolites such as short chain fatty acids (SCFAs) [11], secondary bile acids [12] and microbial-derived tryptophan metabolites [4,7]. Microbial metabolites can then be added back in these systems to test for effects on innate immune responses. As an example, a recent study using antibiotic-treatment demonstrated disrupted migration of neutrophils to the mesenteric lymph nodes from the ileum [13].

Microbiome-derived metabolites

SCFAs

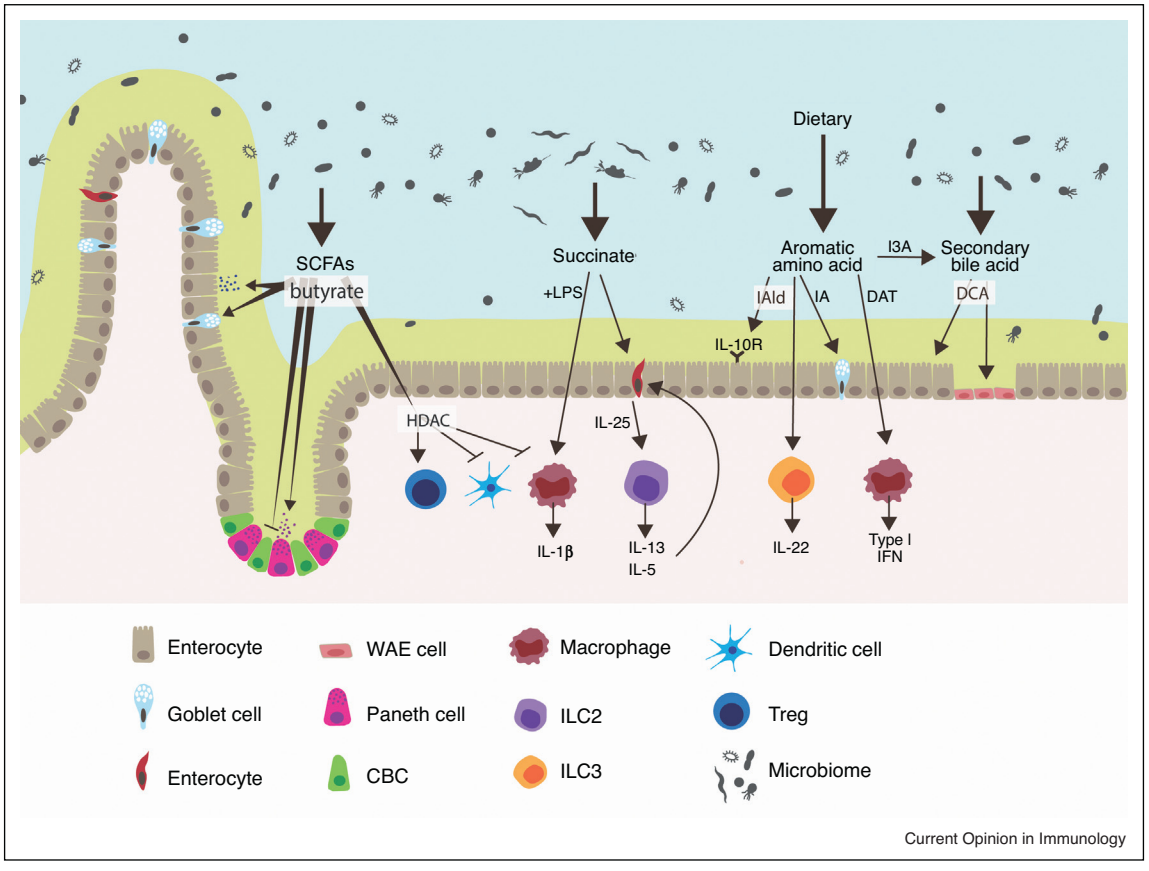
Over the past decade, short chain fatty acids (SCFAs) such as acetate, propionate, and butyrate have been extensively studied, and their roles in host immunity

are well recognized [14]. As one of the most abundant microbial-derived metabolites in the colonic lumen, SCFAs can enter the cells through passive diffusion, carrier-mediated transportation, or engagement of GPCRs [14,15]. SCFAs regulate a variety of processes including modulation epithelial barrier function, inflammation through host innate immune pathways and resistance against enteric pathogens (Figure 1).

Overlying the intestinal epithelial surface is a chemical barrier functionally composed of antimicrobial peptides (AMPs) and mucus that is produced by the specialized IECs Paneth and goblet cells, respectively. Recent studies show that SCFAs enhance both components of this barrier. By acting through GPR43, butyrate induces AMPs such as RegIIIγ and β-defensins in IECs [16]. Other few studies showed synergistic mechanisms between the mucus layer and SCFA-induced AMPs; butyrate not only induces the production of the AMP cathelicidin, but also enhances mucus formation for an optimal innate response against amebic colitis [17]. However, this effect is not universal for all AMPs. Butyrate-induced β-defensin is Muc2-independent as the intestinal mucin inhibited the antimicrobial activity of β-defensin [18]. Further studies are required to carefully characterize the interaction between mucin barrier and other types of AMPs in association with SCFAs (Table 1).

Butyrate also affects the function of epithelial stem cells within colonic crypts. The level of butyrate is far lower at the base of crypts that house epithelial stem/progenitor cells due to the robust consumption of high levels of luminal butyrate by differentiated colonocytes located outside of crypts. Disruption of the normal structure by mucosal injury leads to elevated exposure of stem cells to butyrate which largely impairs their proliferation [19]. The inhibitory effect of butyrate on intestinal stem cells proliferation occurs in part through histone deacetylases (HDAC) regulation of the cell cycle regulator Foxo3 [19,20]. Structure/activity studies revealed that the inhibitory effect of butyrate on HDACs was attributed to its unique molecular structure and strong affinity to Zn^{2+} in the active site of HDACs [20]. For wound repair, we feel that butyrate exposure before barrier reestablishment appropriately brakes intestinal epithelial stem cell proliferation early in this process. This limits stem cell

Figure 1



Mechanisms of action of microbiome-derived metabolites. Examples of known pathways for the microbial metabolite regulation of host physiology and the immune system. Gut microbiome and its metabolites modulate immune signaling through a variety of immune cells as well as intestinal epithelial cells.

Table 1

Microbial metabolites and their effects on host immune system.

Microbial-derived products	Interaction with host innate immunity	References/PMID number	
Short chain fatty acids (Butyrate, propionate and acetate)	Promotes antimicrobial peptides in intestinal epithelium	16 17 18	2018 Mucosal Immunol 2017 Infect Immun 2015 Mucosal Immunol
	Induction of mucus layer	17 23	2017 Infect Immun 2017 J Immunol
	Induces of intestinal epithelial barrier formation	*25865369* *19625695*	*2015 Cell Host Microbe* *2009 J Nutr*
	Induces IL-18 production in intestinal epithelium	*24412617* *25828455*	*2014 Immunity* *2015 Nat Commun*
	Energy source for colonocytes	19	2016 Cell
	Inhibition of intestinal stem cell proliferation	19	2016 Cell
	Anti-inflammatory effects on colonic lamina propria macrophages	21	2014 PNAS
	Facilitates macrophage polarization and function	25 *24412617*	2015 Nat Neurosci *2014 Immunity*
	Potentiate the capacity of DCs to induce extrathymic Treg cell differentiation activity	22 *24412617* *25984582*	2013 Nature *2014 Immunity* *2015 Biochem J*
	Induces retinoic acid production in DCs to modulate adaptive immune responses	*27966553*	*2017 Mucosal Immunol*
	Stimulates the migration of neutrophil	*19335337*	*2009 Clin Sci (Lond)*
	Enhances hematopoiesis of DC and macrophage precursors	*24390308*	*2014 Nat Med*
	Induction of Treg through HDAC	*24226770* *23828891*	*2013 Nature* *2013 Science*
Succinate	Induction of tuft cell-ILC2 circuit and subsequent canonical innate type 2 immune response (goblet cell hyperplasia and hypertrophy and accumulation of ILC2s and eosinophils)	26 27 28	2018 Cell 2018 Immunity 2018 PNAS
	Induction of chemotaxis of macrophages	*28382382* *27481132*	*2017 Diabetologia* *2016 JEM*
	Enhances proinflammatory cytokine production in macrophages	34 35	2013 Nature 2016 Cell
	Induction of migration and proinflammatory cytokine production in DCs	*18820681* 33	*2008 Nat immun* *2015 Cell Rep*
Aromatic amino acid metabolites	Promotes type I interferon response in macrophage	37	2017 Science
	Induces intestinal epithelial barrier function	5 36	2018 Am J Pathol 2017 Nature
	Induces IL-22 production in ILC3	39 40	2013 Immunity 2017 Science
	Enhances proinflammatory cytokine production in macrophages	43	2017 Cell Host Microbe
	Limits neutrophil infiltration	44	2016 Gut Microbes
Secondary bile acid (deoxycholate and lithocholate)	Down regulation of pro-inflammatory genes in the epithelium	47	2018 Gastroenterology
	Regulates proper wound healing in intestinal epithelium	48	2018 Cell Host Microbe
Long chain fatty acids	*NOX4-dependent long chain fatty acid transport and oxidation promotes NLRP3 inflammasome activation in macrophages*	*27455510*	*2016 Nat Med*
	Induces anti-inflammatory responses in macrophages through GPR120	*24997608*	*2014 Nat Med*
Niacin	*Promotes anti-inflammatory phenotypes on colonic macrophages and DCs. Also induces IL-18 in colonic epithelium*	*24412617*	*2014 Immunity*
Retinoic acid	*Regulates proper intestinal epithelial differentiation and function*	*29139475*	*2018 Mucosal Immunol*
	Primes DCs to regulate IL-10-producing Treg cells	*25027601*	*2015 Mucosal Immunol*
	Regulates ILC1 and ILC3 migration	*26141583*	*2015 Immunity*
	Regulate the generation and function of ILC3s	*24670648* *24458645*	*2014 Nature* *2014 Science*
Trimethylamine N-oxide (TMAO)	*Affects macrophage foam cell formation*	*26687352*	*2015 Cell*
	Increases leukocyte adhesion and recruitment to endothelium	*26903003*	*2016 J Am Heart Assoc*

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proliferation during exposure to potentially harmful components within the lumen. With barrier reestablishment, the exposure of stem cells to butyrate is greatly diminished, and they can more safely undergo proliferation to regenerate crypts.

Importantly, HDAC inhibition is a shared biochemical mechanism for SCFA function across diverse cell types. Butyrate exerts anti-inflammatory effects on intestinal macrophages and DCs by inhibiting HDAC [21,22]. One target of HDAC inhibition by SCFAs is IL-10R which has recently been shown to improve barrier function in the intestinal epithelium during mucosal damage [23]. IL-10 was recently reported to modulate the immune response of colonic macrophages through mTOR-dependent NLRP3 inflammasome activation [24]. However, it is not clear whether this pathway is HDAC-dependent. SCFAs also have extra-intestinal effects on innate immunity including the modulation the blood brain barrier and microglia maturation [25]. Together, recent findings have implicated an immune suppressive role of SCFAs on innate immune cells in maintenance of immunological tolerance to commensal microbiome upon crypt injury.

Succinate

Microbially produced succinate, another product largely derived from dietary fiber fermentation has drawn much recent attention due to its role in metabolic homeostasis and intestinal crosstalk between gut microbiome and host immune system [26••,27••,28••,29]. Succinate serves as both an intermediate in TCA cycle and a receptor ligand for the GPCR, SUCNR1 [28,30].

Unlike SCFAs, succinate is found both intracellularly and extracellularly. While commensal microbial-derived succinate can benefit the host as glycolytic fuel [29], enteric pathogens can also take advantage of microbiome-derived succinate and compete with the members of the indigenous microbiome for colonization. Salmonella utilizes bacterial symbiont-derived succinate to complete its TCA cycle and induce inflammation in the gut [31]. One key regulator is the normal microbiome as shown by the well-tolerated, microbial-derived succinate that correlated with low burdens of the parasite, Tritrichomonas under homeostatic state [27,28]. In fact, Tritrichomonas-infected mice become resistant to additional infections [26]. Nevertheless, perturbation of intestinal symbionts by antibiotic leads to dysbiosis, allowing expansion of succinate-producing microbes. Therefore, increased availability of local succinate supports the growth of pathogen such as *Clostridium* difficile [28,32].

Three laboratories recently reported that parasitic-derived succinate elicits robust type 2 innate immune response in the small intestine [26–28]. Both protozoa and helminths produce succinate which elicits expansion of intestinal tuft cells. Tuft cell-derived IL-25 further promotes ILC2 activation and production of type 2 cytokines (e.g. IL-13 and IL-5) which leads to adaptive intestinal remodeling and activation of other immune cells for parasite control [26–28]. Although tuft cells highly express receptors for both SCFAs (FFAR3) and succinate (SUCNR1), only succinate activates the tuft cell-ILC2 circuit [26,27]. Moreover, it is becoming clear that tuft cells have distinct succinate sensing mechanisms for protists and helminths. While succinate-induced type 2 response for protist infection requires SUCNR1, sensing of helminth-derived succinate is largely SUCNR1 independent [27,28]. Further studies are needed to identify the alternative or redundant pathways by which succinate orchestrates the type 2 response in the intestine.

Apart from its expression in epithelial cells, SUCNR1 is also expressed on innate immune cells such as macrophage and DCs [33,34], suggesting a direct regulatory role of succinate in innate immune signaling. Although succinate alone has no effect on cytokine production in macrophages [35], it can synergize with TLRs and drive IL-1β production in the presence of LPS34 [35]. Impaired succinate levels in inhibitor-treated macrophages correlate with reduced IL-1β serum levels in mice during salmonella infection [34]. However, much remains unknown. For example, what other cell types respond to succinate and what are the functional implications of succinate-mediate responses in intestinal inflammation?

Amino acid metabolites

Several recent studies showed that microbiome-derived aromatic amino acid metabolites play an essential role in regulating innate immune responses in both homeostasis and disease states [36••]. While tryptophan-derived metabolites have received the most attention, a recent study focusing on desaminotyrosine (DAT) provided insight into a tyrosine-derived metabolite that modulates the innate immune response to influenza infection through type I interferon signaling [37]. Both host cells and components of the microbiome can metabolize tryptophan into indole derivatives [38]. A variety of intestinal microbes have thus far been identified to generate tryptophan bioactive metabolites [4,39–41], and disrupted microbial tryptophan metabolism contributes to aberrant immune response [39,42,43].

Gut microbial-derived indole derivatives are known to be crucial ligands for aryl hydrocarbon receptor (AhR) signaling pathway which orchestrates innate immune responses upon infection and inflammation. Indole-3-aldehyde (IAId) stimulates IL-22-producing ILC3 via AhR [39,40]. Colonization of IAld-producing bacteria induced ILC enhanced antifungal response against *Candida albicans* in both GF mice and antibiotic-treated mice [39]. In another infection model with *Citrobacter*

rodentium, increased susceptibility was reported in mice with either deficient or constitutively active AhR signaling which can be attributed to their lack of ILC3 [42]. In contrast, supplementing mouse diets with a tryptophan metabolite restored ILC-mediated mucosal protection and greatly improved the outcome of DSS and *Citrobacter rodentium*-induced colitis [39,42].

Recent findings suggest that IAId induced IL-10R1 expression on IECs in a AhR-dependent manner [5]. Similar to IAId, Indole-3-propionic acid (IPA) was demonstrated to fortify the intestinal barrier integrity [36] and ameliorate DSS-induced intestinal inflammation [5]. In addition, a newly identified commensal bacteria, *Peptostreptococcus russellii*, metabolizes tryptophan into metabolites such as indoleacrylic acid (IA) which promote goblet cell function as well as anti-inflammatory cytokine production in macrophages [43]. Furthermore, administration of indole-derived metabolite protects against medication-induced enteropathy by reducing neutrophilic infiltration [44].

In the intestine, host-derived tryptophan metabolites such as kynurenine (Kyn) are produced in the context of both the intestinal epithelium and innate immune cells via enzyme indoleamine 2,3-dioxygenase 1 (IDO1) [4,45•]. Notably, butyrate was reported to induce the expression of IDO1 in DCs [15]. Moreover, a regulatory role of indole-3-acetate (I3A), the conjugate base of Indole-3-acetic acid (IAA) was shown in host bile acid metabolism. Taken together, these findings implied a sophisticated interaction between microbial and host-derived metabolites [7].

Decreased IAA and increased Kyn have been observed in both fecal and serum samples in patients with IBD, suggesting a shift from microbial to host-dominant metabolism in disease state [4,45]. Caspase recruitment domain family member 9 (CARD9), a critical adaptor protein in myeloid PRR signaling and an IBD risk allele, also plays a role in tryptophan metabolism. A recent study reported that GF mice receiving microbiome from CARD9 deficient mice are susceptive to DSS-induced colitis possibly due to the lower level of IAA and impaired IL-22 production in ILCs [4]. The phenomenon can be partially explained by CARD9 effect on microbiome composition which subsequently affect the production of microbial tryptophan metabolites.

Microbial-derived secondary bile acid

Secondary bile acids such as deoxycholate (DCA) and lithocholate (LCA) have recently shown to be important immune modulators of both infection and wound healing. Secondary bile acids are biotransformed from host-derived primary bile acids; their production is solely dependent on the microbiome, and only a few species of bacteria are capable of effecting the biochemical reactions to produce them [8].

Secondary bile acids can have direct effects on microbes as well as innate immune system. As an example of the former, DCA and LCA have direct bactericidal effect on the enteric pathogen *Clostridium difficile* [46]. Thus, these metabolites diminish the ability of this pathogen to colonize a susceptible host. As an example of the latter, secondary bile acids enhance host immune defenses following infection through regulation of innate immune responses. Recent studies showed that DCA rescued genetically susceptible mice infected with *Campylobacter jejuni* by downregulating expression of *C. jejuni*–induced pro-inflammatory genes in IECs [47]. In accordance with these examples, we propose that secondary bile acids may affect other pathogens and the innate immune response to them. Additional systematic studies of bacterial, parasitic and fungal infections will be required.

The innate immune system can also modulate wound repair in the intestine. A recent study demonstrated that the level of local DCA in intestinal mucosal wounds is pivotal for the wound closure by post-mitotic wound-associated epithelial (WAE) cells during the initial barrier re-establishment phase, as well as the proper transition to the subsequent wound channel/crypt regeneration phases in the colon [48]. Depletion of DCA-producing bacteria by antibiotics greatly decreased DCA levels and impaired epithelial proliferation in wound-adjacent crypts during colonic wound repair, whereas DCA reconstitution could rescue the phenotype. Importantly, DCA functioned through classic innate TLR2/MyD88 signaling which is farnesoid X receptor (FXR)-dependent [48]. Future research is needed to investigate how microbial-derived secondary bile acids regulate other cellular components of the innate immune system and the receptors involved during wound repair processes.

Concluding remarks

Even with an accumulating understanding of the influence of microbial metabolites on host physiology and immunity, much remains unknown. The number of metabolites known to have a physiologic effect likely do not encompass the full spectrum of compounds and activities. Improved techniques are, therefore, necessary to study the inaccessible or unknown microbial products. A concern regarding current research is that the animal model systems with their distinct microbiome may not reflect the interplay between humans and their microbiome.

In order to bridge current findings into medically relevant contexts, studies need to be undertaken which reproduce the complex interaction between human life and the microbiome. First, we need to understand the degree to which host genetics shape the composition of

microbiome and the subsequent effects on metabolite phenotypes. *Christensenella minuta*, a SCFA-producing bacterium represents one of the examples that is highly heritable and independent of environmental influence [49]. Furthermore, studying the impact of factors such as diet, disease, pharmacologic intervention, and environment on the microbial metabolite repertoire will be important in understanding the nuanced effects of metabolites on human health. Current evidence shows how further understanding of microbial metabolites will continue to illuminate the complex and important relationship between the microbiome and host immune system. Future therapeutics that emerge from this research may entail specifically designed diets, engineered bacterial communities, or synthetic compounds that recapitulate the positive impact of the microbiome on the immune system.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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