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Microbiome, metabolites and host immunity

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In the intestine, the microbial genomes and repertoire of biochemical reactions outnumber those of the host and significantly contribute to many aspects of the host's health, including metabolism, immunity, development and behavior, while microbial community imbalance is associated with disease. The crosstalk between the host and its microbiome occurs in part through the secretion of metabolites, which have a profound effect on host physiology. The immune system constantly scans the intestinal microenvironment for information regarding the metabolic state of the microbiota as well as the colonization status. Recent studies have uncovered a major role for microbial metabolites in the regulation of the immune system. In this review, we summarize the central findings of how microbiota-modulated metabolites control immune development and activity.

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Introduction

The intestine is a complex ecosystem that is composed of mammalian and prokaryotic components, the latter of which are collectively termed the microbiota. These two elements have coevolved and are in constant interaction through diverse mechanisms.

The intestinal microbiota contributes to multiple physiological processes of the host, including metabolic and nutritional homeostasis, energy expenditure and immunity. A growing number of studies in recent years suggested that the microbiome is playing a crucial role in immune development and function of the host as well as the host metabolic state. This function is to a large part achieved through the exchange of small molecules between the intestinal lumen and the host's mucosal surfaces, as well as the systemic circulation [1].

The mammalian intestine harbors a diverse array of metabolites that have the potential to modulate immunity. The microbiome can synthesize, modulate and degrade a large repertoire of small molecules, thereby providing a functional complementation to the metabolic capacities of the host. In particular, the microbiota can metabolize dietary components that cannot be metabolized by the host such as complex carbohydrates [2]. Moreover, the bacterial metagenome contributes to the production of primary metabolites and the modulation of secondary metabolites that affect host physiology in multiple ways. Several such microbial metabolic pathways have been associated with host physiology, including the production of fatty acids, vitamins, neuroactive metabolites and amino acids, with beneficial effects ranging from epithelial homeostasis, immune cell development and neuronal regulation to nutrient digestion [3].

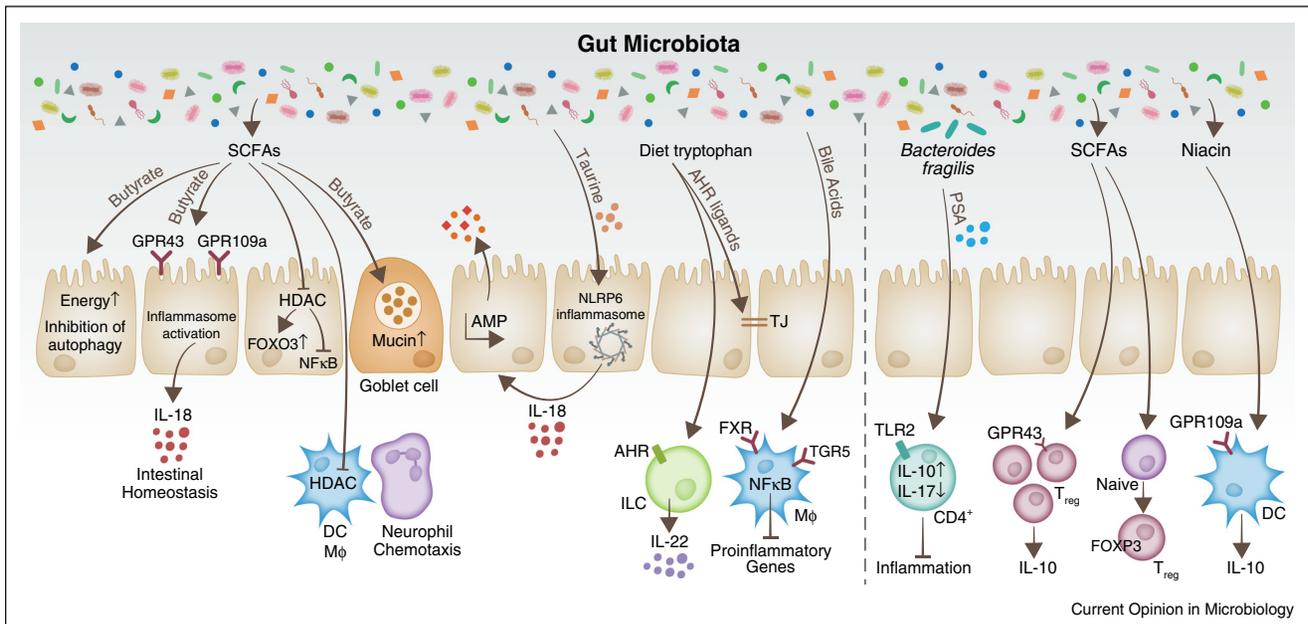
Elucidating the function of microbial metabolites that modulate the host physiology requires identification of metabolites that differ between healthy and disease states. When the balanced interaction between the host and the microbiota is disrupted, intestinal and extra-intestinal diseases may develop. Multiple studies have identified such metabolites that are differentially abundant in health versus disease. Some of these identified metabolites, including short-chain fatty acids (SCFAs) and indoles, were shown to have a protective effect from the development of disease [4], while others, such as trimethylamine N-oxide (TMAO) and 4-ethylphenylsulfate (4-EPS), were shown to directly drive the susceptibility to disease [5,6].

The effects of microbiome-modulated metabolites on metabolic and other host physiological functions are highlighted elsewhere [7,8]. Here, we highlight key metabolites that are formed or modulated by the gut microbiota and describe their effects on the different arms of the host immune system (Figure 1).

Metabolite interactions with innate mechanisms of defense

The immune system and the microbiota are two components that influence one another to orchestrate host physiology as well as to maintain a stable microbiome community. The mammalian host recognizes microbial presence and activity through a number of germ-line encoded microbial sensors called pattern recognition receptors (PRRs). Such receptors are able to recognize microbial structure and effector molecules [8,9]. Microbial metabolites serve as an additional layer of communication between the host and the microbiota.

Figure 1



Modulation of immune signalling through microbial metabolites. Examples of metabolites that are produced or modulated by the intestinal microbiota, and their impact on the intestinal immune response. Metabolite effects are either direct on immune cells, or relayed by the intestinal epithelium.

The identification of specific microbiota-derived metabolites and their effect on the immune system have provided mechanistic insight into colonization mechanisms and immune cell-microbiota co-regulation (Table 1).

The interaction between the host's innate immune system and the microbiome through metabolites spans multiple cell types. Although not considered a classical immune cell, epithelial cells of the intestine are an integral part of the mucosal immune system as they are equipped with innate PRRs and contribute to intestinal homeostasis through bacterial recognition [10]. As part of the mucosal immune system, epithelial cells provide an innate mechanism through which the host develops and maintains a stable healthy microbiota composition, while preventing pathogen entry. To this end, epithelial cells are equipped with a large anti-microbial arsenal of effector mechanisms and undergo intense communication with the myeloid and lymphoid cells in the local environment [11]. Interestingly, the influence of the microbiota on intestinal epithelial cells strongly couples immunological and metabolic functions, as evidenced in particular by the role of a common bacterial metabolite, short-chain fatty acids (SCFAs).

SCFAs are the result of non-digestible carbohydrates fermentation by anaerobic commensal bacteria. The host recognizes SCFAs, namely acetate, propionate and butyrate, through the G-coupled-receptors GPR41, GPR43

and GPR109a [4,12]. SCFAs have been found to function as energetic substrates for epithelial cells. Butyrate has been reported to regulate energy metabolism in intestinal epithelial cells [13], as colonocytes can utilize bacterially produced butyrate as a primary energy source. Consequently, colonocytes of germ-free mice display an energy-deprived state and enhanced autophagy that can be rescued by butyrate supplementation [13]. Recently, butyrate was identified as an inhibitor of intestinal stem cells [14]. Butyrate suppresses proliferation by acting as a histone deacetylase (HDAC) inhibitor therefore allowing for increased promoter activity of the negative cell-cycle regulator Foxo3 during injury. Butyrate utilization by enterocytes limits the access of butyrate to the intestinal crypts, thereby protecting stem cells from the anti-proliferative effect during homeostasis [14]. This study suggests that SCFAs contribute to the maintenance of the epithelial barrier. Epithelial cells integrity is further achieved through the SCFA acetate, which was shown to enhance the protection against infections [15]. Other studies showed that supplementation with SCFAs contributes to the preservation of mucosal immunity through goblet cells as these cells up-regulate the expression of MUC genes in response to butyrate [16].

An integral part of innate immunity is the immune sensing complex called inflammasome [17]. A recent study suggests that high-fiber diet, which activates GPR43 on intestinal epithelial cells, results in activation of the NLRP3 inflammasome leading to its assembly and

Table 1

The effect of microbiota-modulated metabolites on the host.

Metabolite	Effect on the host	Source	Reference
Short chain fatty acids (butyrate, acetate, propionate)	Regulate energy metabolism in intestinal epithelial cells and preserve mucosal immunity Increase the numbers of colonic Tregs and enhances the regulatory function of Tregs in the large intestine through epigenetic regulation Inhibit intestinal stem cell proliferation. Butyrate suppresses proliferation by acting as a histone deacetylase (HDAC) inhibitor Enhance the protection against infections Activates GPR43 and GPR109a on intestinal epithelial cells, result in activation of the NLRP3 inflammasome leading to production of IL-18 Shape microglial phenotype and functions NF- κ B inactivation and suppression of pro-inflammatory cytokines and nitric oxide in neutrophils and mononuclear cells through HDAC inhibition	Non-digestible carbohydrate fermentation by anaerobic commensal bacteria	[13–16,18,25–29, 47,55**,56–58]
Niacin	Induces anti-inflammatory properties in DC and macrophages in a GPR109a-dependent manner and suppresses colonic inflammation	Diet and microbiota	[58]
Indole	Induces IL-22 secretion by ILCs, further driving the secretion of antimicrobial peptides and protection from infections by pathogens Epithelial barrier enhancement	Commensal bacteria metabolism of tryptophan	[34**,36,37]
Retinoic acid	DC induction of gut-homing lymphocytes Supports the development of Tregs through TGF- β and suppresses the development of T _H 17 cells During inflammation, RA is required for the induction of a proinflammatory CD4 ⁺ helper T cell response	RALDH-expressing cells of the host	[40,41,59,60]
Polysaccharide A (PSA)	Suppresses the production of pro-inflammatory IL-17 and promotes expression of IL-10 by CD4 ⁺ T cells	Produced by the commensal <i>Bacteroides fragilis</i>	[46–48]
Bile acids	Regulation of bacterial growth Inhibit the induction of pro-inflammatory genes through NF- κ B	Host bile acid secretion and bacterial bile acid metabolism	[52,53*,54**]
Taurine	Nlrp6 inflammasome activation and contribution to intestinal homeostasis	Host bile acid secretion and bacterial bile acid metabolism	[22]

the downstream production of IL-18 [18]. Additional metabolites were shown to contribute to intestinal homeostasis through the modulation of inflammasome signaling in epithelial cells. NLRP6, a member of the NOD-like receptor family, which is highly expressed in intestinal epithelial cells and involved in the maintenance of an intact mucus layer, viral recognition, as well as inflammasome formation [19–21]. The activation of the NLRP6 inflammasome is influenced by the microbiota-modulated metabolites taurine, histamine, and spermine, thereby regulating the level of epithelial IL-18 production, antimicrobial peptide secretion, and intestinal community composition [22]. Hence, in addition to pattern recognition of microbial cell components alone, the metabolic activity of the microbiome is likewise sensed by the immune system, and this sensing results in an anti-microbial response directed at maintaining a stable colonization. In the absence of microbial recognition, this pathway is disturbed leading to the development of dysbiosis and inflammatory disease manifestations [23,24].

In addition to their effect on intestinal epithelial cells, SCFAs contribute to intestinal homeostasis through several hematopoietic cell types. Leukocyte function and neutrophil chemotaxis are influenced by SCFAs [25], as the exposure of neutrophils and mononuclear cells to SCFAs inhibits HDAC activity leading to NF- κ B inactivation, and suppression of pro-inflammatory cytokines and nitric oxide [25,26]. A similar suppression of HDAC that result in anti-inflammatory phenotype was observed in dendritic cells (DCs) and intestinal macrophages [27]. It was shown that butyrate and propionate inhibit DC generation from bone-marrow precursors, through their transportation into the cells by Slc5a8. The expression of the transcriptional regulators PU.1 and RelB was reduced upon SCFA-mediated DC development arrest [28]. Furthermore, SCFAs have a profound impact on DC-dependent immunity. Mice fed high-fiber diet present a shift in the microbiota composition, as reflected by a change in the Firmicutes to Bacteroidetes ratio. These mice present elevated SCFAs level in the circulation and

are protected from allergic challenge while low-fiber fed mice develop an allergic-associated lung inflammation [29]. Treatment with the SCFA propionate enhanced DC seeding of the lungs and promoted T_H2 functions. This anti-inflammatory DC effect, which is primarily mediated by propionate, is dependent on GPR41 (but not GPR43) activity [29].

While the molecular mechanisms by which the microbiome controls epithelial cell function remain largely unknown, several examples have been found that highlight the involvement of specific bacterial-derived metabolites in the regulation of intraepithelial lymphocyte function [30,31]. One such example is the microbial metabolism of tryptophan. In the intestine, bacteria can metabolize tryptophan to active substances. For example, *Escherichia coli* is a classic producer of indoles that can serve as a 'quorum-sensing' signal. Indole signals regulate the virulence and biofilm formation of both *E. coli* and other bacteria, and typically have a beneficial effect in the intestine [32,33]. It was shown that commensal Lactobacilli utilize tryptophan as an energy source to produce ligands of the aryl hydrocarbon receptor (AhR), such as the metabolite indole-3-aldehyde [34**]. AhR is a ligand-activated transcription factor and a powerful modulator of the immune response with broad effects on the development, organogenesis of intestinal lymphoid follicles (ILF), as well as the proliferation and activation of immune cells [34**]. AhR was found to be necessary for the maintenance of the epithelial barrier and the homeostasis of intraepithelial lymphocytes (IELs) [30,31]. In a dextran sodium sulfate (DSS)-induced colitis model, AhR-deficient mice presented enhanced disease susceptibility compared to control mice [31], which was not apparent when mice were fed a synthetic diet depleted of dietary AhR ligands. The transfer of functional IELs to AhR-deficient mice resulted in ameliorated disease and enhanced recovery [31].

AhR is expressed by several immune cell types including ROR γ ⁺ group 3 innate lymphoid cells (ILC3s) that are involved in ILF genesis, and the expression of AhR on ILC3s is functionally required for cell expansion [35**]. In addition, AhR can induce IL-22 secretion by ILCs and this further drives the secretion of the antimicrobial peptides lipocalin-2, S100A8, and S100A9, and protects from the pathogenic infection by *Candida albicans* [34**]. Similarly, in the absence of AhR, mice are more susceptible to infection with *Listeria monocytogenes* and *Citrobacter rodentium* [36,37].

Recently tryptophan metabolites were shown to regulate inflammation both locally in the intestine and in the central nervous system. Lamas *et al.* found that mice deficient in caspase recruitment domain 9 (CARD9) were susceptible for intestinal inflammation and microbiota from CARD9-deficient mice was lacking tryptophan-catabolizing capability that can be reversed by

supplementing the mice with Lactobacillus strains [38]. Furthermore, Rothhammer *et al.* found that tryptophan metabolites can modulate astrocyte activity and central nervous system inflammation through activation of AhR signaling [39].

The promotion and development of both the regulatory and inflammatory arms of innate immunity are suggested to be influenced by additional metabolites, such as retinoic acid (RA), a vitamin A derivative. RA was shown to be important for the expression of gut homing molecules on immune cells. In the absence of TLR signaling in MyD88-deficient mice, intestinal DCs express low levels of retinal dehydrogenases, a critical enzyme for RA biosynthesis, and are impaired in their ability to induce gut-homing lymphocytes [40]. In colonized mice, RA-associated genes are highly expressed in peripheral lymph nodes (pLN), but strongly reduced in germ-free mice. A wave of RA producing CD45⁺ CD103⁺ RALDH⁺ DCs was shown to invade the pLN of colonized mice shortly after birth or in germ-free pLNs following co-housing with colonized mice [41]. Adoptive transfer of these cells restored cellular defectiveness in secondary LNs of germ-free mice. It was discovered that these DCs orchestrate the homing of lymphocytes to pLN in early neonatal weeks. In adult mice fed a vitamin A deficient diet, this process was disrupted, suggesting a connection between gut microbiota, vitamin A and immune maturation of peripheral lymph nodes [41].

The effect of the microbiota on host immunity is also prominent in the central nervous system (CNS). Microglia, phagocytic mononuclear cells that are derived from the yolk sac during embryonic development, invade the CNS and represent the resident immune population of the brain and spinal cord. In a pioneering study by Erny *et al.* [42], the effects of gut microbiota on microglia gene expression and function were examined. Transcriptome analysis revealed distinct gene expression profile of germ-free-derived microglia compared to microglia isolated from colonized mice. The expression of several M1-related genes, such as Il-1 α , Cd14, Cd86 and Fcgr1 were significantly increased in germ-free-isolated microglia compared to colonized mice. Microglia were more abundant in the brains of germ-free mice and represented different morphology featuring enhanced ramification. Furthermore, a similar microglial phenotype was observed when conventional mice were treated with antibiotics. When germ-free mice were co-housed with colonized mice or treated with a mix of SCFA, the phenotype was reversible, suggesting a role for gut microbiota-derived SCFAs in shaping microglial phenotype and functions [42].

With respect to SCFAs, microglia express the G-protein coupled receptor GPR109a, which binds nicotinic acid (niacin) and the SCFA butyrate. It was shown that

GPR109a levels are increased in the substantia nigra of Parkinson's disease (PD) patients, in cells that co-localized with microglial markers [43]. Furthermore, niacin index (NAD/NADP) was lower in PD patients, and associated with enhanced pain episodes and decreased deep sleep duration [43]. Another study examined the effect of the metabolite β -hydroxybutyric acid (BHBA) on mesencephalic neurons. BHBA treatment inhibited LPS-induced [3 H]dopamine uptake and neuronal cell death *in vitro* [44]. In a PD rat model where LPS was intranigally injected, BHBA treatment reduced microglia activation, enhanced neuronal survival and improved motor skills of the treated rats. GPR109a possibly mediated this effect, via NF- κ B inhibition in microglia, resulting in reduced pro-inflammatory responses (TNF- α , IL-1 β , IL-6) [44].

Together, these studies suggest that microbiota-modulated metabolites have a major effect on host innate immunity, however much remains unclear regarding the causative link between microbiota-associated metabolites and innate immune modulation in health and disease.

Metabolite interactions with adaptive mechanisms of defense

Commensal microbiota shape not only the innate immune response, but also the adaptive arm of intestinal immunity. Germ-free mice display an undeveloped adaptive immune system [45]. Although the molecular mechanisms by which the microbiota controls the development of the immune system are still largely unknown, several bacterial-derived metabolites were shown to be involved in the regulation of adaptive immune cell development, in particular T lymphocytes.

In order to maintain intestinal homeostasis, the immune system must be tolerant towards antigens derived from commensal microbiota, a task that is partially achieved through inducible regulatory T cells (Treg), which produce the anti-inflammatory cytokine IL-10. Bacterial molecules participate in the preservation of tolerance and immunity in mucosal surfaces through the promotion of Treg-mediated anti-inflammatory responses. The bacterial polysaccharide A (PSA) produced by the commensal *Bacteroides fragilis* has an effect on the development of inflammation. PSA suppresses the production of the pro-inflammatory IL-17 and promotes expression of IL-10 by CD4 $^+$ T cells through binding to TLR2 [46], thus inhibiting inflammation. In a trinitrobenzene sulfonic acid (TNBS)-induced colitis model, PSA-treated mice had higher numbers of Tregs with suppressive capacity [47], and similarly suppressed colitis following *Helicobacter hepaticus* colonization [48].

Another group of intestinal metabolites with colitis-modulating ability are bile acids. Bile acids are produced

in the liver from cholesterol, and are further metabolized by the gut microbiota [49]. Germ-free mice display reduced diversity of secondary bile acids compared to colonized mice [50]. The gut microbiota controls bile acid signaling through the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (GPBAR1) or TGR5. Mice lacking FXR show bacterial overgrowth and disrupted epithelial barrier, suggesting that FXR may have a protective role through the regulation of bacterial growth [51 \bullet]. Furthermore, bile acid signaling was suggested to contribute to the effects of the microbiota on the metabolic syndrome [52]. In addition, the host immune response is also modulated by bile acids, which inhibit the induction of pro-inflammatory genes through NF- κ B [53 \bullet]. Bile acids diversity also affects the response of adaptive immune cells in inflammatory bowel disease (IBD). When fed saturated fatty acids that induce alterations in bile acids metabolism, IBD-susceptible IL-10-deficient mice displayed enhanced T $_H$ 1 responses and increased colitis [54 $\bullet\bullet$]. The changes in bile acids composition were accompanied by expansion of a low-abundance, sulphite-reducing pathobiont, *Bilophila wadsworthia*.

Another group of metabolites with a profound impact on Treg biology are SCFAs, discussed above for their effect on the innate immune system. SCFAs were shown to affect the regulation of inflammation through Treg homeostasis [55 $\bullet\bullet$]. Several studies have demonstrated that SCFAs produced by members of the intestinal microbiota, in particular Clostridia, increase the numbers of colonic Tregs and enhance the regulatory function of Treg cells in the large intestine [47,56]. SCFAs administration to germ-free mice increased the numbers and IL-10 expression of FOXP3-expressing Tregs, in a GPR43-dependent manner [55 $\bullet\bullet$]. Butyrate-induced differentiation of Tregs results in ameliorated colitis severity. Mechanistically, butyrate epigenetically enhances histone H3 acetylation in the promoter and conserved non-coding sequence regions of the *Foxp3* locus [57]. Thus, the down-regulation of inflammatory capacity in the intestine is a mechanism through which the host and the microbiota maintain tolerance in the complex micro-environment of the intestine.

In addition to being the receptor for butyrate, GPR109a is also the receptor for intestinal niacin. The microbial-derived butyrate and niacin engage GPR109a on epithelial cells, macrophages and DCs, and trigger the secretion of IL-18 from epithelial cells, and IL-10 from DCs and macrophages, which further leads to suppression of inflammation, as IL-10 favors the development of Tregs from naïve CD4 $^+$ cells [58].

In contrast to SCFAs, long-chain fatty acids have been reported to support T $_H$ 1 and T $_H$ 17 cell differentiation and proliferation [58].

The regulation of intestinal adaptive immunity is also dependent on other metabolites from diverse chemical groups. For instance, RA was shown to promote the development of both regulatory and inflammatory arms of adaptive immunity. Similar to SCFAs, RA supports the development of Treg cells through TGF- β and suppresses the development of T_H17 cells [59]. In contrast, during inflammation, RA is required for the induction of a proinflammatory CD4⁺ helper T cell response [60].

In addition to vitamin A, additional vitamins participate in the modulation of the immune response. Vitamins from groups B and K, for which the host is dependent on the microbiota for biosynthesis, have been reported to influence the biology of T cells. For example, *Bifidobacterium* and *Lactobacillus* are critical for the synthesis of vitamin B9 [61], which is a survival factor for Tregs.

RA was further shown to modulate the activity of additional cell types, in particular B cells. IgA is the most abundant antibody in the gut, neutralizing toxins derived from luminal bacteria and shifts the gut microenvironment into an anti-inflammatory direction, favoring the growth of commensals. IgA is generated by class switching recombination (CSR) process in either T cell-dependent, or independent pathways, both of which involve the assistance of DCs and the involvement of the gut microbiota. In germ-free mice, IgA levels in the lamina propria are substantially reduced, while quickly restored upon colonization [62]. DCs participate in IgA CSR by supplying B-cell activating factor (BAFF), a proliferation inducing ligand (APRIL) [63], and the metabolite RA mediates this process. Recently it was shown that gut bacteria and RA are involved in DCs-dependent IgA CSR even in remote organs such as the lungs. CD103⁺ and CD24⁺ lung dendritic cells produce TGF- β as a result of TLR/MyD88-dependent microbial stimuli. RA is essential for upregulation of CCR9 and the α 4 β 7 integrin, directing antigen-specific B cells to the gut to protect against intranasally-administered pathogens, suggesting a complex immune-metabolite-bacterial interplay between the lungs and the gut [64]. TGF- β and RA produced by lamina propria DCs are also known to promote differentiation of ROR γ t-expressing Tregs which in turn produce IL-10 that prevent activation of pro-inflammatory cells [65].

Concluding remarks

While the recognition of the presence of the microbiota by pattern recognition receptors is well established [66], recent studies have demonstrated that the mucosal immune system of the host is also capable of sensing the metabolic state of the microbiota through microbial metabolites recognition. The microbiota is capable of metabolizing both host-derived and diet-derived metabolites through a range of biochemical reactions that magnify the metabolic capabilities encoded by the genome of

the host and has an important role influencing many aspects of health and disease. It has become increasingly apparent that the microbiota, through metabolites production, modulates signaling pathways that contribute to mucosal immune homeostasis. The diversity of metabolites with immune-modulatory function outlined in this review demonstrates that the metabolites impact on host physiology ranges across a wide range of chemical groups and target cells. Additional work is required to fully determine the physiological role of these metabolites and the entire spectrum of microbial metabolites that participate in orchestrating host immunity. The discoveries made in the microbiome field in the last decade have broadened our understanding of the evaluation of the microbial colonization state and metabolic activity through secreted metabolites. There is a need for well-controlled studies that will mechanistically link metabolites to diseases beyond association and will highlight the potential of the microbiota for disease prevention. Furthermore, the development of new technologies will allow analyzing metabolite signature as a screening tool for disease as a therapeutic approach to human disease.

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