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SUPPLEMENT ARTICLE

Interkingdom Communication and Regulation of Mucosal Immunity by the Microbiome

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Intercellular communication and environmental sensing are most often mediated through ligand-receptor binding and signaling. This is true for both host cells and microbial cells. The ligands can be proteins (cytokines, growth factors, and peptides), modified lipids, nucleic acid derivatives and small molecules generated from metabolic pathways. These latter nonprotein metabolites play a much greater role in the overall function of mucosal immunity than previously recognized, and the list of potential immunomodulatory molecules derived from the microbiome is growing. The most well-studied microbial signals are the nonmetabolite microbe-associated molecular pattern molecules, such as lipopolysaccharide and teichoic acid, that bind to host pattern recognition receptors. Here, we will highlight the immunomodulatory activities of other microbiome-derived molecules, such as short-chain fatty acids, bile acids, uric acid, prostaglandins, histamine, catecholamines, aryl hydrocarbon receptor ligands, and 12,13-diHOME.

Keywords. Microbiota; Dendritic Cell; Metabolite; T Regulatory Cell.

Mucosal barriers are the hub for interkingdom communication between the microbiota and host. The microbiome plays a significant role in modulating the function of mucosal barriers and immunity, including the mucosa of the gastrointestinal tract, upper and lower airways, and urogenital tract. This interkingdom communication occurs at a molecular level through the production of metabolites by microbes (and host), and the subsequent sensing of those metabolites by the host (and microbes), via metabolites binding to specific receptors and generating intracellular signals. However, some microbial metabolites, such as acetate and vitamins, can also affect host biochemistry directly (without receptor binding). We are not discussing those interactions in the current review. Microbial metabolites can modulate inflammatory processes locally in the mucosa and can also diffuse (or be actively transported) across the epithelium, where they can enter the systemic circulation and affect inflammatory processes in distal organs. This brief review will provide examples of how various microbiota-derived metabolites can affect epithelial barrier function, antigen presentation, and regulatory T-cell (Treg) responses on the mucosa.

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METABOLITES: THE LANGUAGE OF INTERKINGDOM COMMUNICATION

Short-chain fatty acids (SCFAs), such as butyrate or propionate, are bacterial metabolites produced following the fermentation of dietary fiber or resistant starches by specific anaerobic bacteria, typically in the large intestine. While butyrate remains largely in the intestine, propionate can be found in the circulation as well as the intestinal mucosa. Butyrate and propionate bind to the host receptors FFA2, FFA3, and GPR109a, which are expressed on the host epithelium, as well as a number of other cell types, including macrophages and dendritic cells (DCs) [1–4].

Bile acids include primary and secondary bile acids. Primary bile acids are produced in the liver of the host through cholesterol breakdown and then metabolized by bacteria in the intestine to produce a variety of secondary bile acids. Primary and secondary bile acids bind and activate a series of cell-surface or nuclear receptors, which include farnesoid-x-receptor (FXR) and G protein bile acid receptor (GPBAR1 or TGR5) [5]. Bile acids can also signal through other receptors with differing affinities and activation abilities, depending on the receptor.

Uric acid is created by host cells from the purine derivatives xanthine and hypoxanthine via the enzyme xanthine oxidase. Uric acid crystallizes and is bound by a number of host binding proteins, as well as a causing cellular damage. It is a potent activator of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and is responsible for the adjuvant effects of alum [6]. Bacterial members of the microbiota have the metabolic capacity to produce uric acid via other pathways

and intestinal colonization by yeast, such as *Saccharomyces cerevisiae*, can enhance purine metabolism and uric acid production by host intestinal epithelial cells [7, 8].

Prostaglandins are lipids enzymatically derived in host tissues from the 20-carbon polyunsaturated fatty acid, arachidonic acid, via the action of cyclooxygenases and specific synthases. Two critically important prostaglandins in the regulation of innate and adaptive immunity, as well as epithelium function, are prostaglandin E_2 and D_2 (PGE_2 and PGD_2) There are a number of host receptors for these prostaglandins, including EP1, EP2, EP3, EP4, DP1, and DP2 (CRTH2). In addition to host cells, fungi (including yeast found in the microbiome) are capable of producing prostaglandins and related bioactive lipids (oxylipins), all of which can modulate host immune cell activity [9]. While these pathways can be sensitive to various cyclooxygenase inhibitors, the specific enzymes involved in prostaglandin production from fatty acid precursors by yeast still remain to be identified. The literature on the immunomodulatory effects of prostaglandins, including PGE_2 and PGD_2, is extensive and beyond the scope of this review; however, the concept that the microbiome may directly contribute to prostaglandin-mediated regulation of mucosal immunity is an emerging field [10–12].

Histamine is derived from the decarboxylation of the amino acid histidine via the enzyme L-histidine decarboxylase. There are at least 4 host receptors for histamine (H1R, H2R, H3R, and H4R). The activities of histamine are quite broad and range from immune modulation to fluid movement in tissues, sleep and gastric acid secretion. Histamine is one of a number of vasoactive biogenic amines that can be produced by host cells, found in food, or produced by bacterial members of the microbiome [13]. There is increasing evidence that bacteria-derived histamine plays a role in regulating mucosal immunity.

Catecholamines are another class of biogenic amines produced by both the host and the microbiome [14]. They are created enzymatically starting from phenylalanine or tyrosine and include epinephrine, norepinephrine and dopamine. In the host, they can act locally on cells, in synapses as a neurotransmitter, or systemically as hormones. Host receptors for catecholamines include dopamine receptors (D1, D2, D3, D4, and D5) and adrenergic receptors (α1, α2, β1, β2, and β3). Macrophages have been recognized as a local source of catecholamines during inflammation that can act to augment innate inflammation [15]. Bacteria-derived catecholamines serve as quorum-sensing molecules that can modulate various pathogenic pathways in bacteria, including promoting infection [16, 17].

Aryl hydrocarbon receptor (AHR) ligands regulate many aspects of mucosal and systemic immunity, including T-cell and dendritic cell biology [18]. AHR is a cytoplasmic receptor and transcription factor that serves as a receptor for a variety of small molecules, which induce AHR activation. These ligands include host-derived tryptophan metabolites such as kynurenine, kynurenic acid, xanthurenic acid and cinnabarinic acid. The metabolic activity of the intestinal microbiome also provides a source of AHR ligands, including indole, indole-3-acetate, and tryptamine. AHR activation also modulates the composition of the intestinal microbiota, thereby playing an important role in host-microbe homeostasis [19].

12,13-diHOME is a linoleic acid metabolite whose biological activities are not well characterized. The production of this molecule by the host has been implicated in worsening asthma and in alterations in lipidogenesis. Peroxisome proliferator-activated receptor γ can serve as a receptor for 12,13-diHOME. Bacteria in the gut microbiome, such as *Enterococcus faecalis* and *Bifidobacterium* spp., have been shown to encode epoxide hydrolase genes that are capable of generating 12,13-diHOME [20]. Bacterial-derived 12,13 DiHOME can act on dendritic cells to promote Th2 inflammation in mice undergoing allergen challenge by decreasing Treg numbers in the lungs [20].

HOST MUCOSAL RESPONSES TO MICROBIAL METABOLITES

Microbial metabolites can affect the activity of mucosal structural cells and submucosal leukocytes in the tissue, as well as in distal sites. This includes effects on innate immunity and adaptive immunity. Here, we will highlight the effect of microbial metabolites on the intestinal epithelium, antigen presenting cells, and Tregs.

Intestinal Epithelium and Barrier Function

The intestinal epithelium is composed of epithelial cells and various secretory cells that form a dynamic, permeable barrier that allows selective absorption of nutrients while restricting access of luminal antigens and pathogens to the underlying submucosal tissue. Mucus layers cover the apical surface of the intestinal epithelium and the microbiota is found in the outermost layer of the mucus, as well as in the lumen. Intercellular tight junctions (TJs) impart barrier function to the gut epithelium and control the movement of solutes between intestinal epithelial cells, as well as contributing to cell polarity. The TJ backbone is comprised of junctional adhesion molecules, claudins, occludins, and zonula occludens proteins.

Microbial metabolites are critical contributors to gut homeostasis and can have a positive or negative effect on gut integrity and barrier function. The expression and/or function of TJs can be modulated by microbiome-derived metabolites such as SCFAs, prostaglandins, uric acid, and histamine [21]. Butyrate can enhance epithelial cell survival by serving as the major metabolic substrate for colonocytes, providing approximately 60%–70% of their energy requirements necessary for epithelial cell proliferation and differentiation. Supplementation of butyrate or propionate can induce expression of mucin messenger RNA. Butyrate supplementation also accelerates the assembly of occludin and zonula occludens 1, thereby enhancing barrier function [22]. Histamine can

induce edema in the submucosal tissue underlying the epithelium, resulting in fluid movement back into the lumen without evident change in the integrity of intercellular junctions [23].

In studies of colitis in a murine model, treatment with uric acid alone could worsen disease and increase gut permeability and *S. cerevisiae* colonization of the intestine enhanced host purine metabolism, leading to an increase in uric acid production and worsening barrier function [7]. Mice colonized with *Candida albicans* have increased intestinal permeability in a model of food allergy [24]. As noted earlier, *C. albicans* can also produce PGE_2 and other oxylipins; high levels of PGE_2 can decrease barrier function, presumably by compromising TJs and/or inducing Th2-mediated inflammation [10–12, 25]. However, it should also be noted that *C. albicans* can also secrete a cytolytic peptide toxin (candidalysin) that triggers membrane pore formation, epithelial cell damage and subsequent immune cell recruitment. Candidalysin has been shown to drive immunopathology in the oral and vaginal mucosa. However, the role of candidalysin secretion in enhanced gastrointestinal tract permeability in the absence of inflammation remains to be determined [26].

Antigen Presentation and Inflammasome Activation

Dendritic cells, macrophages, and B cells are the professional antigen-presenting cells) of the immune system and their activity can be modulated (up or down) through the activation of pattern recognition receptors by microbe-associated molecular pattern molecules; activation of the inflammasome by uric acid, bile acids, and SCFAs; and modulation of differentiation pathways by bacterial metabolites. Bacterial members of the microbiota have the metabolic capacity to produce uric acid and intestinal colonization by yeast, such as *S. cerevisiae*, can enhance host purine metabolism and uric acid production [7, 8]. The C-type lectin receptor Clec12A is a myeloid cell–expressed inhibitory receptor that acts as a cell damage/death sensor, largely by detecting uric acid crystals. Its activation can limit proinflammatory pathways by limiting Syk activation but, in dendritic cells, promotes the production of type I interferons via the engagement of Src kinase and up-regulation of Tank-binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF3) signaling [27].

The secondary bile acid lithocholic acid can inhibit NLRP3 inflammasome and interleukin 1β production in macrophages by signaling through TGR5, resulting in the ubiquitination and degradation of NLRP3 [5]. Both FXR and TGR5 appear to play a role in controlling inflammation, because enhanced inflammation develops in both FXR and GPBAR1 knockout mice in various disease models. NLRP3 can also be activated by SCFA binding to GPR43 on colonic epithelial cells, largely owing to the stimulation of K+ efflux and cellular hyperpolarization [3]. The SCFA butyrate can modulate the differentiation, maturation and function of dendritic cells and macrophages; it can also inhibit interleukin 12 production while significantly inducing interleukin 23 expression [28, 29]. Treatment of mice with the SCFA propionate can modulate bone marrow hematopoiesis, including generation of myeloid (macrophage and DC) precursors via GPR41 (FFAR3) [2]. Propionate-altered DC precursors are less reactive and display an impaired ability to promote T-helper (Th) type 2 (Th2) responses.

Regulatory T Cells and Down-regulation of Mucosal Inflammation

CD4 Tregs express the transcription factor Foxp3 and are critical for regulating inflammation at mucosal surfaces. Tregs can develop in the intestinal mucosa and periphery, if the proper signaling milieu is present. Tregs have the capacity to down-regulate the inflammatory potential of other T-helper subsets via secretion of interleukin 10 and transforming-growth factor β and, in the absence of Tregs, mucosal inflammation (Th1, Th2, or Th17 mediated) is markedly enhanced. Butyrate and propionate can promote Treg development in the intestine and periphery and SCFA-producing clostridial species of the microbiome, notably Lachnospiraceae, promote Treg accumulation in the intestine [30]. Treatment of naive T cells with butyrate (under Treg-inducing conditions in vitro) blocks the deacetylation of the histone H3 promoter and conserved non-coding regions of the Foxp3 locus [31]. Generation of Tregs in the periphery can be potentiated by propionate, which is also capable of histone deacetylase inhibition [1].

SCFAs have also been shown to induce expression of the vitamin A–converting enzyme RALDH1 in epithelial cells from the small intestine and DCs in the draining lymph nodes, which was correlated with increased numbers of intestinal Tregs and increased levels of luminal immunoglobulin A, indicating the development of tolerogenic mucosal DCs under these conditions [32]. While GPR109A is a receptor for SCFA, it is also a receptor for niacin (which can also be produced by gut microbiota). Niacin and GPR109A signaling can promote anti-inflammatory properties in colonic macrophages and DCs and induce the differentiation of Tregs. Gpr109a also plays a role in butyrate-mediated induction of interleukin 18 in colonic epithelium [33]. In addition to SCFA effects that modulate Treg numbers and function, bacterial-derived 12,13 DiHOME has been proposed to act on dendritic cells to decrease Treg numbers [20].

In addition to SCFA, microbiome-derived histamine can modulate mucosal immunity. One study's findings suggested that microbiome-derived histamine could act through NLRP6 inflammasome signaling, epithelial interleukin 18 secretion, and anti-microbial peptide production [34]. While histamine is historically studied as a host-derived mediator, bacteria can also produce histamine and histamine-secreting microbes are present within the human gut microbiome [13]. Histamine can also suppress DC chemokine and inflammatory cytokine production. Histamine-secreting *Lactobacillus* species were described >50 years ago [35], and more evidence is accumulating

for the protective role of bacterial-derived histamine in down-regulating mucosal inflammatory diseases [13].

Th17 cells and type 3 innate lymphoid cells are critical for the maintenance of the barrier through their secretion of effector cytokines like interleukin 22 and interleukin 17. However, the improper balance of Th17 and Tregs can lead to Th17 driven inflammation. The AHR is highly expressed by both Th17 cells and type 3 innate lymphoid cells. Indole-3-aldehyde is an AHR ligand derived from bacterial metabolism of dietary tryptophan that can enhance production of interleukin 22 by $NKp46^{+}$ cells in the Peyer's patches of the gut to provide antifungal resistance by driving Th17-mediated inflammation [36]. The microbiome-derived secondary bile acid 3-OxoLCA can repress Th17 cells by inhibiting Th17 differentiation through direct binding to the Th17 transcription factor RORyt [37]. Microbial products from *Lactobacillus* species and other bacteria, such as tryptophan metabolites, indole-3–pyruvic acid, urolithin A, SCFAs, and dihydroxyquinoline, also have the potential to modulate inflammation via AHR-dependent mechanisms [38].

CONCLUSIONS

Metabolites, both host derived and microbiome derived, are the "language" of interkingdom communication on the mucosa and function via ligand-receptor interactions. One facet of this dialogue is the generation and maintenance of immune tolerance to the microbiome. One of the pitfalls in the field of in vivo metabolomics research is the difficulty in attributing the relative contributions of immunomodulatory metabolites, whether they are host derived or microbe derived, and the effects of diet, environment, and genetics on their levels in the mucosa. In addition, while this review is focused on mucosal immunity of the host, metabolic cross-talk between kingdoms will also affect individual members of the microbiota and its overall composition, which can further contribute to changes in mucosal immunity. We have now come to appreciate that a "fringe benefit" of microbiome-mediated mucosal tolerance is that mucosal tolerance of allergens, foods, and some xenobiotics also depends on this interkingdom communication within the host.

Notes

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