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The bidirectional nature of microbiome-epithelial cell interactions

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Abstract

The biogeography of the mammalian intestine is remarkable in that a vast microbial consortium exists inside the organism, surrounded by intestinal epithelial cells. The microbiome and the intestinal epithelium have developed a complex network of interactions that maintain intestinal homeostasis. We now recognize that functions of the epithelium are compartmentalized in specific intestinal epithelial cell subtypes. Furthermore, we are beginning to understand the ways in which microbes and their metabolic products impact the specific epithelial subsets. Here, we survey the mechanisms utilized by the microbiome to regulate intestinal epithelial function, and inversely, how different epithelial cell subtypes cooperate in regulating the microbiome.

Introduction

The ability for the microbiome to alter and manipulate physiology and morphology of the host intestine has been appreciated for decades [1]. However, as we enter the age of single-cell biology [2••], it is becoming apparent that treating the intestinal epithelium as a homogeneous layer of cells is grossly inappropriate. Furthermore, as the use of conditional Cre-lox systems continues to be developed, we gain a more nuanced appreciation of how individual cells regulate host–microbiome interactions that was never before possible. Indeed, the intestine is composed of a great variety of intestinal epithelial cell (IEC) subtypes, each with their own specialized reciprocal relationship with the microbiome (Table 1). All IECs originate from the intestinal stem cell which divide into transit amplifying cells (TACs) that serve as intermediates between the stem cell and the terminally differentiated IEC [3]. TACs subsequently populate the intestine with the various IEC subtypes following commitment towards a secretory or absorptive lineage [4]. Paneth cells, goblet cells, tuft cells, and enteroendocrine cells, which release large amounts of antimicrobial peptides (AMPs), mucins, type 2 immune mediators, or hormones, respectively, are derived from the secretory lineage [4]. Meanwhile, enterocytes and colonocytes, which are major nutrient absorbers, and Microfold (M) cells, which act principally in microbial antigen uptake, are derived from the absorptive lineage [4].

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Herein, we lay the foundation for future research working to interrogate cell-specific host-microbiome interactions, by reviewing seminal data that exemplifies prominent ways in which particular epithelial cell functions affect the microbiome and reciprocally, how the microbiome affects particular epithelial cell functions. Although our review is not an exhaustive list of all previously described interactions, we touch upon common themes and conceptual modules of cell-specific host-microbiome interactions.

Inside-out: cell type-specific regulation of the microbiome

The large intestine houses the highest number of bacteria in terms of quantity and diversity, so the existence of a reciprocal relationship between the microbiome and colonocytes becomes immediately apparent. Perhaps the best described interaction involves the microbial production of short-chain fatty acids (SCFAs), which colonocytes use as fuel [5]. SCFA metabolism by colonocytes promotes aerobic respiration, maintaining the hypoxic environment of the large intestine that most commensals require [6]. In the absence of SCFA, colonocytes undergo anaerobic respiration releasing oxygen and nitrates into the lumen that facilitate the expansion of pathogens such as *Escherichia coli* and *Salmonella* [7••]. In contrast to mature colonocytes, TACs exhibit low basal oxygen consumption [8], leading to increased availability of oxygen and nitrate, allowing for facultative anaerobic bacteria, such as *E. coli*, to expand in ulcerative colitis mouse models [9–11]. These phenotypes are also present in ulcerative colitis patients, and may contribute to disease pathology [12].

Along the same lines, host enterocytes can provide carbon sources utilized by host commensals. While mucus had long been conceptualized simply as a lubricant for fecal matter moving through the gastrointestinal tract, it is now clear that mucus acts as a medium for the colonization of commensal organisms to maintain immune homeostasis [13]. The highly glycosylated mucins that constitute a major architectural component of the mucosal layer are primary carbon sources for some commensals, like *Akkermansia muciniphila* [14], whose abundance is inversely correlated with severity of metabolic and inflammatory diseases [15–17]. Lipid modification, such as sialylation of mucin glycans, have also been recently described as metabolic resources for commensals like *Ruminococcus gnavus* [18•]. Indeed, mucin remains an important modality whereby goblet cells feed microbes, some requiring the fermentation products of their neighbors [19]. Fucosylation of small intestinal IEC also is utilized as fuel for the microbiome, including *Bacteroides*, in times of starvation [20]. Feeding commensals, which colonize the mucus layer and hoard potential resources that pathogens could use otherwise [21], may represent a colonization resistance strategy of the host, by which the function of the microbiome is used to prevent infection.

Additionally, initiation of IEC inflammatory cascades can result in an antimicrobial response, modulating the bacterial composition. By virtue of their role as producers of AMPs [22], Paneth cells inherently have a strong influence over microbial composition in the small intestine. Both chemical and genetic depletion of Paneth cells in mice resulted in robust and long-lasting changes in the microbiome, including a significant reduction of *Proteobacteria* [23]. Furthermore, the most abundant antimicrobial peptides produced by humans, a-Defensin-5, is shown to have direct bactericidal activity towards several members

of the human microbiome, and can therefore alter bacterial communities in *vivo* [24]. More generally, Paneth cells maintain species-specific microbiome communities, as transgenic expression of human defensins in mice results in large shifts in detectable bacteria [25].

Goblet cells sense pathogen-associated molecular patterns (PAMPs) in the gut and maintain the mucosal barrier accordingly. TLR-dependent signaling and microbial metabolites trigger the NLRP6-dependent inflammasome in goblet cells to stimulate mucus production [26–28]. Furthermore, it was recently shown that neuronal-derived IL-18 is responsible for driving goblet cell production of antimicrobial peptides upon infection [29•]. These recent findings, together with the prior literature, demonstrate how crucial microbial responses of goblet cells are to reinforce barrier integrity.

Tuft cells also indirectly regulate the gut microbiome during type 2 immune responses. By triggering ILC2s to release IL-13, tuft cells can engage IL-13-responsive goblet cells to release mucus to brush away not only eukaryotic but also bacterial pathogens. Tuft cell derived IL-25 has also shown protection against cancer-associated dysbiosis [30]. How tuft cells communicate, and with whom they communicate with to maintain barrier integrity is certainly a growing field of interest with much to be explored.

As the major epithelial mediators of antigen uptake, M cells are especially critical for regulating the microbiome. Conditional deletion of RANKL using villin-Cre results in loss of M cells in mice [31]. Although these mice showed similar levels of microbial diversity in the intestine, the levels of IgA-coated bacteria increased [31]. IgA-coating has previously been shown to mark bacterial members of the microbiome with strong inflammatory capacity [32]. Transient depletion of M cells, however, has been shown to increase the levels of segmented filamentous bacteria (SFB), demonstrating that M cells regulate ileal SFB abundance [33••].

Situated at the bottom of intestinal crypts are the intestinal stem cells (ISCs). While undergoing continuous proliferation, new daughter cells migrate upwards along the crypt-villus axis towards the gut lumen and differentiate into the many specialized cell types along the way in a controlled manner [34]. While the majority of gut microbes are situated in the mucosal layer above the villi, a subset of microbes called the crypt-specific core microbiota are maintained within the crypt in close proximity to the stem cell niche [35]. The abundances of various crypt-associated and mucosa-associated microbes have been correlated to colon cancer development [36].

In all, various IEC subtypes exert regulation over the microbiome. Nearly all described microbiome effects from IEC have been studied in the context of a single IEC subtype. However, it would be interesting to understand if and how IEC subtypes communicate with each other to coordinate responses towards the microbiome. Furthermore, given that most of the work only measures microbial abundances, it is likely that deeper levels of microbiome regulation by epithelial cell subsets escape our current knowledge, for example, at the level of commensal transcriptomes.

Outside-in: cell type-specific regulation by the microbiome

The microbiome utilizes diverse mechanisms to influence the intestinal epithelium, which can be organized into a few discrete conceptual modules. A major form of communication is through pattern recognition receptor (PRR) signaling, for example, in Paneth cells. The fact that germ-free (GF) animals have lower levels of AMP production and decreased Paneth cell number is evidence of microbial regulation of Paneth cell differentiation and function [37,38]. One such mechanism involves activation of Paneth cell AMPs via MyD88 signaling, a downstream adaptor of several PRRs [39•]. In fact, loss of MyD88 results in a number of defects in the intestinal epithelium, including decreased mucin production, suggesting PRR signaling in goblet cells also influences their behavior [40].

Beyond PRRs, several IEC subtypes also express receptors that can respond to microbial metabolites, circumventing the need to sense bacteria directly, by instead monitoring a metabolite proxy for the state of intestinal microbial colonization. In addition to the impact of SCFAs on enterocyte metabolism as discussed above, a recent report [41] identified microbial metabolites regulating epithelial lipid metabolism. L-lactate from *Lactobacillus paracasei* enhances lipid storage by inhibiting beta-oxidation, while *Escherichia coli*-derived acetate promotes beta-oxidation. Paneth cells can also be affected by similar microbial metabolites. Microbial-derived lactic acid is capable of signaling through GPR81 on Paneth cells to increase Paneth cell number [42••].

Tuft cells are also known to respond to the microbiome, as antibiotic-induced dysbiosis resulted in tuft cell hyperplasia [30]. Using single-cell transcriptomics, intestinal tuft cells were recently shown to specifically express *Sucnr1 and Ffar3*, receptors for the microbially derived metabolites succinate and SCFAs, respectively [43•]. Parasite-derived succinate has been shown to activate type 2 immune responses by tuft cells [44]; however, recent evidence extends this finding to commensal bacteria-derived succinate [34]. Interestingly, one group identified a tuft cell hyperplasia phenotype in germ-free mice colonized with helminth-free microbiota, while goblet cell hyperplasia was not simultaneously observed [45]. Altogether, these studies implicate tuft cells in responding to bacterial presence in the intestinal mucosa, broadening their roles described in anti-parasitic responses, which have been the major focus of tuft cell research (Figure 1).

Enteroendocrine cells (EECs), the largest endocrine system in the body [46], express receptors that are sensitive to microbial products such as SCFAs [47•], indole [48], secondary bile acids [49], and structural components of the microbial membrane [50], allowing the microbiome to exert control over host metabolism. Moreover, butyrate released by spore-forming bacteria upregulates serotonin (5-HT) synthesis by EECs [51]. Germ-free mice consequently have lower levels of 5-HT [52], leading to abnormal colonic motility. Indeed *Clostridia*-derived cellular components can also induce 5-HT secretion [53]. Besides 5-HT, EECs also secrete anorectic gut hormones such as Peptide YY (PYY) and glucagon-like peptide (GLP-1) [46]. PYY is a satiety factor that inhibits food intake and gastrointestinal motility, while GLP-1 is an incretin hormone [54]. In primary colonic cell cultures and enteroendocrine model cell lines, PYY production has been found to be strongly stimulated by butyrate and propionate [47•]. However, a separate report finds that

GF mice had upregulated functional capacity in their EECs, increasing PYY production and secretion [55], suggesting GLP-1 resistance. This discrepancy could be due to differences in model systems, but could also be attributed to differences in protease activity. For example, a recent study found that genera such as *Prevotella* or *Lactobacillus* express enzymes similar to dipeptidyl peptidase IV (DPP-4), the enzyme responsible for GLP-1 and PYY breakdown [54]. This can then serve as a feedback loop, as decreasing DPP-4 leads to altered microbiota composition and microbial metabolite abundance [54].

Models of bacterial infection have uncovered several mechanisms implicating microbial metabolites, reactive oxygen species, and PAMPs as stimuli driving ISC proliferation [56,57]. Interestingly, while microbial-derived butyrate was found to suppress ISC proliferation, lactate stimulated ISC differentiation [42••]. Furthermore, *Lactobacillus*-derived indole metabolites, which signal through aryl hydrocarbon receptor (AhR) on epithelial cells, can also induce ISC proliferation [58]. *Peptostreptococcus*-derived tryptophan metabolites, which also can signal through AhR, similarly induce goblet cell proliferation [59]. Additionally, the microbiome can have profound effects on the cellular composition of the intestinal epithelial layer by polarizing the differentiation of TACs [60].

Furthermore, bacteria and bacterial antigen can directly interact with IECs. M cells have long been known to endocytose microbial antigen, and it has been demonstrated that commensals utilize M cells to maintain tolerance [61]. Despite the critical role of M cells in regulating bacterial antigen in the intestine, GF mice have no loss in M cells [62]. This is particularly interesting, as it is known that Peyer's patches, where M cells typically reside, are underdeveloped in GF animals [63]. Although commensals have no apparent role in M cell development [62], pathogens appear to influence their cellularity, as M cell numbers increase following *Salmonella* infection [64]. These data would imply that the intestine maintains a pool of M cells poised to respond to antigen, and upon pathogenic challenge, the host responds by increasing the sites of antigenic uptake.

In addition to M cells, enterocytes also seem to endocytose microbial antigens. Recently, it has been shown that SFB antigens are taken up by IECs in a clathrin-dependent manner, which is required for the induction of antigen-specific T_H17 cells [65]. Furthermore, in colonocytes, tumorigenesis can be mediated by direct interactions with microbes. Several groups have shown reduced tumor formation in several mouse models of colorectal cancer (CRC) inGFmice[66]. The abundancesofseveral members of the microbiome have been shown to correlate with CRC in humans, the most prevalent being *Fusobacterium* species [67]. Although mechanistic understanding is incomplete, recent reports demonstrate that *Fusobacterium* produce a virulence factor, FadA, capable of binding E-cadherin on colonocytes to induce cell proliferation via Wnt/β-catenin signaling [68,69].

These direct bacterial-epithelial interactions also occur in other IEC subtypes. Goblet cells are capable of delivering soluble antigens from the gut lumen via goblet cell-associated antigen passages (GAPs) to tolerogenic $CD103^+$ dendritic cells [70]. The enteric pathogen *Salmonella* Typhimurium was shown to inhibit GAPs during infection [71]. Interestingly, while goblet cell hyperplasia has been associated with parasitic infections [72], bacterial

infections, including *Citrobacter rodentium*, have been associated with the depletion of goblet cells [73], suggesting their significant role in maintaining barrier integrity.

Overall, IECs can sense their microbial environment to regulate diverse processes. These interactions typically occur via PRR recognition of bacterial ligands, or sensing of microbe-specific metabolites, such as SCFA. In general, the level of IEC response correlates to the severity of signal. For example, PRR signaling indicative of pathogenic crypt invasion results in enhanced AMP expression and mucin production. Metabolite sensing, on the other hand, can communicate to IECs without pathogenic invasion of the microbe, resulting in a wider range of both pro-inflammatory and anti-inflammatory responses. Given the large abundance of potential metabolite sensors in humans [74,75], it is possible we are only scratching the surface of microbiome-mediated IEC regulation.

Conclusions and perspectives

The regulatory nature of the microbiome and specific cell types in the intestine is inherently reciprocal. Direct recognition of bacterial molecules, for example through PRRs, can result in proliferation of epithelial cells, and production of antibacterial proteins. Metabolic byproducts from bacteria can alter epithelial activation states, and metabolic byproducts of the epithelia can alter bacterial composition.

Recent studies have uncovered a profound impact of the microbiome on fundamental cell biological processes of IECs, including protein turnover [76] and circadian rhythms [77–80], suggesting that several additional features of host–microbiome interactions remain to be uncovered.

As research in host-microbiome interactions progresses, more emphasis should be placed on cell-type specific responses. Although the use of germline-transgenic and pan-epithelial Cre-lines has unmistakably enhanced our understanding of host-microbe interactions, utilization of cell-specific Cre-lines that allows for the dissection of exact cellular mechanisms will provide clarity. Such models have been enabled by recent large-scale single cell transcriptome, mass cytometry, and spatial profiling studies that identified more comprehensive lists of cell type-specific genes, and have also revealed novel IEC cell states and subpopulations [81,82]. It is also clear that significant differences in microbiome diversity exist between laboratory-maintained and wild mice [83]. Experimental designs that account for this may help to address concerns of reproducibility in studies of host-microbiome interactions. Taking advantage of all such resources will allow us to refine our understanding of bidirectional host-microbiome interactions and their impacts on human health. This information can be useful in the treatment of several etiologies with underlying epithelial dysfunction, such as inflammatory bowel disease and cancer.

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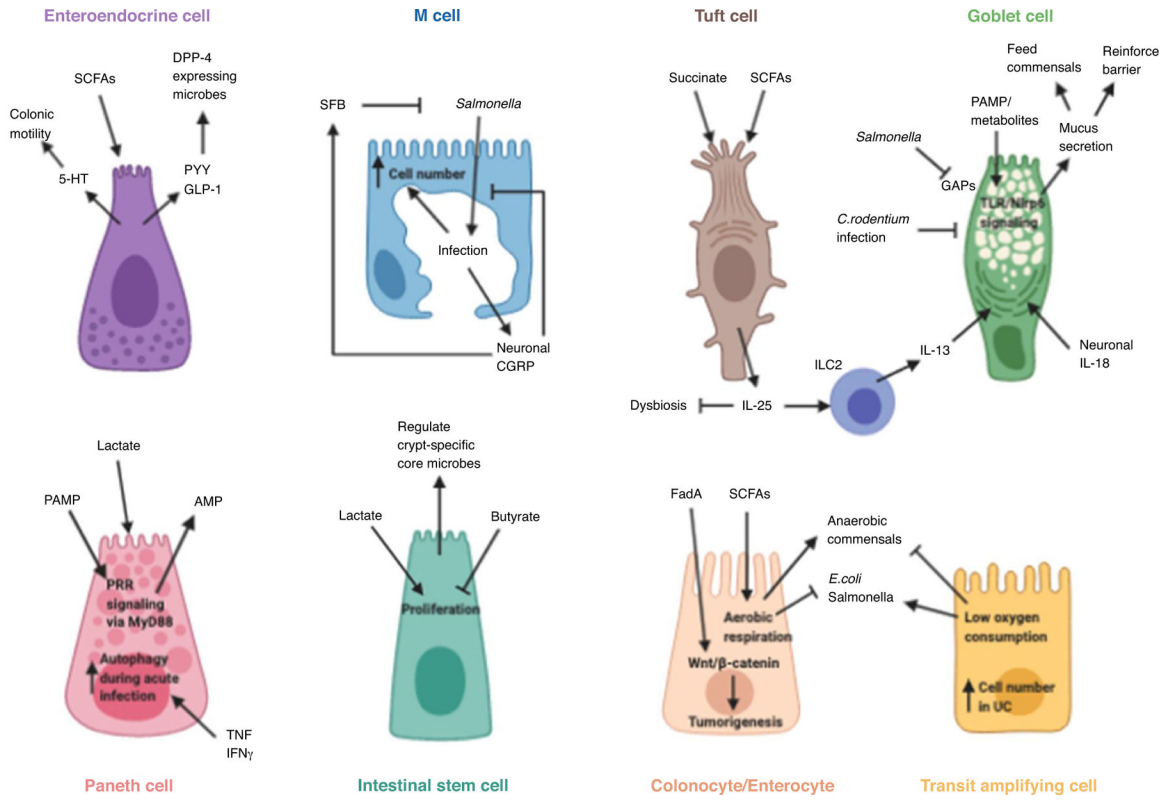

Figure 1. The reciprocal interactions of microbiome and IEC.

A number of different modules define the relationships between host cell and microbe. Metabolites, for example, can initiate and enhance physiological functions of immune cells, such as EECs, tuft cells, colonocytes, and Paneth cells. Reciprocally, host effector molecules, such as AMPs from Paneth cells, or mucins from Goblet cells, can alter microbiome composition.

Table 1

Summary of IEC subtype function and localization

Cell type	Primary canonical functions	Location	Interactions with microbiome
Intestinal stem cells	Replenish the epithelial cell layer every ~4–5 days	Small intestine Colon	Microbiome-derived lactate stimulates ISC proliferation
Goblet cells	Secrete mucins and other factors into the gut lumen; goblet cell-associated antigen passages	Small intestine Colon	Provide a carbon source to bacteria in the form of mucus
Paneth cells	Secrete antimicrobial peptides into the mucosa; support the stem cell niche of the crypt	Small intestine only	Alteration of microbial colonization niche through antimicrobial peptides,
Tuft cells	Trigger type 2 immune responses against parasites	Small intestine Colon	Stimulation by microbiome-derived succinate
Enteroendocrine cells	Release hormones in response to a variety of stimuli	Small intestine Colon	5-HT production in response to SCFA stimulation
M cells	Uptake of luminal antigens and delivery to the Peyer’s patches	Small intestine only	Uptake of microbial antigen, regulation of SFB levels
Enterocytes	Physical barrier; nutrient absorption; epithelial cell shedding	Small intestine only	Endocytosis of microbial antigen. Microbiome-derived lactate and acetate regulate chylomicron release
Colonocytes	Physical barrier; nutrient absorption; epithelial cell shedding	Colon only	Metabolism of microbiome-derived SCFAs, provide glycans as a carbon source to bacteria