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## Resident commensals shaping immunity

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### Abstract

All animals coexist with myriad commensal microorganisms in a symbiotic relationship that plays a key role in health and disease. Continuous commensal–host interactions profoundly affect the development and regulation of the host’s immune system. The complex interaction of the commensal microbiota with the immune system is a topic of substantial interest. An understanding of these interactions and the mechanisms through which commensal microbes actively shape host immunity may yield new insights into the pathogenesis of many immune-mediated diseases and lead to new prophylactic and therapeutic interventions. This review examines recent advances in this field and their potential implications not just for the colonized tissues but also for the entire immune system.

### Introduction

Vertebrates [1] and invertebrates [2] harbor a complex population of microorganisms (the *microbiota*) colonizing mucosal and non-mucosal surfaces. Two important projects—the Human Microbiome Project (HMP) [3] and the European Metagenomics of the Human Intestinal Tract (MetaHIT) Project [4]—have analyzed human-associated microbial communities and their genes (the *microbiome*). The human microbiota, which has coevolved with the host, comprises mainly bacteria but also harbors other microbes, including fungi [5,6], viruses [7,8], archaea [9], and protozoa. Although the majority of commensals reside in the gastrointestinal tract, distinct microbial communities occupy other parts of the body, including the oral cavity [10,11], respiratory tract [12], and urogenital tract [13,14]. This beneficial host-specific microbiota is required for healthy development of the host’s immune system [15].

Metagenomic studies have revealed the dynamic nature of the commensal microbiota. The microbiome varies among individuals and can fluctuate within the same individual because of environmental factors such as age, health, diet, and geographic location [16,17]. However, gene sequence orthologs and assigned functionality indicate that 50% of the microbial genes in one human’s microbiome are shared by the microbiomes of other humans. Differences in microbiota composition may translate into differences in host physiology and may affect susceptibility to various diseases—inflammatory (inflammatory bowel disease, Crohn’s disease, colon cancer) [18], metabolic (diabetes, obesity, metabolic syndrome, kwashiorkor) [19–21], allergic (asthma, atopy) [22,23], autoimmune (celiac disease, arthritis, multiple sclerosis) [24], and psychological/neurologic (autism) [25].

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The evolution of host–microbiota symbiosis is based on interactions that benefit both parties. The host provides a nutrient-rich environment for the microbiota; commensal microbes secrete metabolites by nutrient processing, prevent infections by pathogenic microbes, provide signals to induce healthy immune development, and stimulate innate and adaptive immune responses to maintain homeostasis [26–28]. Within the gastrointestinal track, host-commensal interactions in distinct compartments like small intestine or colon are regulated variably due to differences in the microbial load and unique morphologies of these tissues. Disturbance of this fine balance (*dysbiosis*) may cause perturbed inflammatory responses resulting in a range of diseases. (Figure 1)

## Commensals induce development of the immune system

Studies with germ-free mice show that absence of the microbiota causes developmental defects in many bodily systems, including the immune system. Germ-free animals, which have a small intestine of decreased surface area, a thinner lamina propria (LP), a larger cecum, fewer plasma cells and intraepithelial lymphocytes, lower IgA levels, and smaller Peyer’s patches and mesenteric lymph nodes (MLNs) than conventional animals, exhibit increased susceptibility to pathogenic bacteria [29,30]. Many of these deficiencies are corrected by recolonization—even in adulthood—with a normal microbiota.

Microbial colonization of the host begins during birth. In humans, changes in the microbiota’s diversity are most significant during the first three years [17] but continue throughout life. The hygiene hypothesis originally proposed that reduced exposure to microbes early in life (i.e., in urban environments and hygienic living conditions) increases susceptibility to immune-mediated diseases, with improper immune-system development due to insufficiently diverse antigenic challenge [31]. However, basic assumptions about the causes of abnormal immune-system development leading to increased disease susceptibility have since been modified. Convincing data now implicate alterations in the microbiome as the most likely culprit in immune-system immaturity and imbalance. The change in the human microbiome over the past half-century is perhaps related to epidemiologic factors that were recognized as significant by the hygiene hypothesis but also may be associated with factors such as the overuse of antibiotics, the presence of antibiotics in food, and hormonal exposure through food and drugs. In an important study, Olszak et al. demonstrated an increase in the number of invariant natural killer T (iNKT) cells in the colonic LP and lungs of adult germ-free mice, with consequent susceptibility of these animals to colitis and allergic lung inflammation. Protection was restored only by microbial colonization of neonatal—not adult—mice. This study clearly indicated a role for early microbial exposure in reducing disease susceptibility [32]. Russell et al. showed that antibiotic treatment of neonatal mice reduces gut-microbiota diversity and that this reduction is associated with increased susceptibility to experimental allergic lung inflammation [33].

## Commensal interactions with epithelial barriers

Epithelial barriers form the first line of defense against pathogens [34–36]. Amar et al. found that when the integrity of the epithelial barrier is compromised by a high-fat diet, commensal bacteria translocate to the blood and adipose tissue in a Nod1-dependent manner. Probiotic bacteria that increase epithelial integrity reduce translocation [37]. The gut epithelial barrier is composed of tightly attached epithelial cells (enterocytes, goblet cells, Paneth cells, microfold cells, and enterochromaffin cells), antimicrobial products, and a mucus layer. Commensals maintain the integrity of epithelial cells, stimulate them to secrete mucus and antimicrobial peptides (AMPs), and thereby contribute to maintaining a basal level of steady-state host defense. Goblet cells secrete mucin-2, which forms a net-like mucus layer physically separating most of the microbiota from the epithelium. In the colon,

the mucus has two layers. The lower layer is dense, is relatively free of bacteria, and has concentrated levels of AMPs (such as  $\alpha$ -defensins produced by Paneth cells); the upper layer is looser and contains some commensal bacteria [38]. In the small intestine, the mucus is only one layer thick and the epithelium is protected from the microbiota by antibacterial proteins such as RegIII, which is secreted by enterocytes in response to MyD88-dependent microbial signals [39]. Furthermore, systemic administration of flagellin, a Toll-like receptor (TLR) 5 ligand, results in interleukin (IL) 22-dependent RegIII expression. (The mechanism involves expression of large amounts of IL-23 by CD103+ CD11b+ LP dendritic cells (DCs), which drives IL-22 expression [40].)

## Commensals stimulate immune cell activation

Through continuous dialogue with host immune cells, commensals maintain the homeostatic balance of the immune system, enabling it to fend off pathogens while tolerating commensals. During eons of coevolution, commensals and immune cells have developed fine-tuned mechanisms to maintain this balance. In addition to inducing development or recruitment of host immune-cell subsets, the microbiota may affect the function of these subsets.

### IgA-secreting plasma cells

Among the most important commensal–host symbiosis mechanisms is microbe-dependent production of secretory IgA by plasma cells, with consequent control of the luminal microbiota. Plasma cells are generated in the germinal centers of Peyer’s patches, and formation of germinal centers depends on microbial stimulation. Plasma cells produce high-affinity IgA, which is shuttled from the LP to the lumen through epithelial cells and binds to the intestinal microbiota and microbial antigens [41]. Fritz et al. showed that, in addition to IgA, plasma cells produce inducible nitric oxide synthase and tumor necrosis factor  $\alpha$ ; production of these antimicrobial mediators requires microbial exposure, and their deficiency in B-lineage cells results in reduced IgA production, gut microbiota dysbiosis, and susceptibility to *Citrobacter rodentium* infection [42]. IgA diversity in B cells depends on somatic hypermutation (SHM) and class-switch recombination (CSR) of their V(D)J gene repertoire. This diversification process induced by continuous exposure to the commensal microbiota requires activation-induced cytidine deaminase (AID). Wei et al. generated mice carrying a knock-in AID point mutation (G23S); they had less SHM but normal CSR function. Although they produced normal amounts of immunoglobulin, their microbiota was abnormally expanded and they were more susceptible than wild-type mice to microbial toxins [43]. Similarly, in PD1-deficient mice, increased numbers of follicular helper T cells lacking the inhibitory receptor PD-1 cause dysregulated B-cell selection, production of low-affinity IgA, dysbiosis, and autoimmunity due to immune overstimulation by the microbiota [44].

### DCs and macrophages

To maintain homeostasis and prevent infections, resident phagocytes closely monitor tissues with close microbial contact. CX3CR1+ macrophages and CD103+ DCs in the intestinal LP have developed mechanisms for avoiding exacerbated responses to commensal bacteria, yet can respond to infection by pathogens. In one mechanism by which commensals are distinguished from pathogens, mononuclear phagocytes residing in the LP do not respond to TLR ligands but do constitutively produce pro-IL-1 $\beta$ , and pathogenic bacteria—but not commensals—can induce IL-1 through the NLRC4 inflammasome [45]. In addition, the microbiota instructs the immune system to inhibit trafficking of bacteria to MLNs via CX3CR1<sup>hi</sup> cells; this mechanism, which depends on MyD88, allows bacterial compartmentalization in the steady state and results in tolerance of commensal bacteria [46].

However, in infection or dysbiosis, CX3CR1<sup>hi</sup> cells, which were previously thought to be non-migratory, traffic microbial antigens to MLNs in a CCR7-dependent manner. CD103<sup>+</sup> DCs are more efficient than CXCR1<sup>+</sup> cells in sampling luminal antigens via their intraepithelial dendrites. After antigen uptake, CD103<sup>+</sup> DCs recruit more DCs, transport antigens or bacteria to MLNs, and induce T cells by antigen presentation. CX3CR1<sup>+</sup> cells, in contrast, are important for sampling soluble luminal antigens [47].

## T cells

Different T-cell subsets are induced by specific commensal microorganisms. If homeostasis is to be maintained, proinflammatory and immunomodulatory effects of these subsets must be in balance. Some commensal microbes have an especially strong impact on T-cell responses. For instance, in the intestine, *Clostridium* species [48,49] and *Bacteroides fragilis* can induce IL-10-producing regulatory T cells (Tregs) [50,51], whereas segmented filamentous bacteria (SFB) are associated with induction of IL-17-producing Th17 cells [52,53]. T-cell stimulation also occurs in other tissues independent of the gut microbiota. Resident commensals in the skin induce local Th17 and Th1 responses that mediate protection from bacterial infections [54].

Although a number of commensal bacterial species induce gut immune responses, *B. fragilis* polysaccharide A (PSA) is the only known symbiosis factor that mediates gut homeostasis by directing cellular and physical immune development [55], stimulating Tregs [51], and providing protection from diseases like colitis [51] and experimental autoimmune encephalomyelitis [56]. The mechanism of PSA recognition and signaling culminating in activation of T cells is not yet fully understood. Pure PSA is specifically recognized in a TLR2-dependent manner [57], internalized by DCs, and presented by major histocompatibility class II molecules to activate T cells [55]. Round et al. reported that pure PSA stimulates IL-10 production through TLR2 on CD4<sup>+</sup> T cells, with no requirement for DCs [58]. Recently, however, the same group demonstrated that, when PSA is associated with outer-membrane vesicles, DCs are required to induce IL-10-producing T cells [59]. Further work will determine exactly how PSA recognition and signaling induce T cell-mediated responses.

Other lymphocytes whose roles are modified by commensal bacteria include iNKT cells, natural killer (NK) cells, and innate lymphoid cells (ILCs). As mentioned above, the commensal microbiota inhibits expression of the CXCL16 gene in host epithelial cells, thereby suppressing iNKT cell activation [32]. Abnormal NK-cell function resulting in sensitivity to viral challenge has been observed in germ-free mice. Microbiota-derived signals stimulate cytokine secretion—required for NK cell priming—from mononuclear phagocytes [60,61]. In the intestine, ROR<sup>+</sup> ILCs constitutively express IL-22, which is important for AMP expression and anti-apoptotic molecule induction. IL-22 production is regulated by the commensal microbiota through induction of IL-25 from epithelial cells, which in turn act through DCs to suppress ROR<sup>+</sup> ILCs [62].

## Conclusions

Studies on the role of commensal bacteria in maintaining immune homeostasis and promoting the host's health have expanded vastly. Commensal bacteria and commensal antigens offer significant potential in therapy for a range of immune-mediated diseases. Transplantation of the fecal microbiota from the gut of healthy donors restores components of the normal intestinal flora, curing patients with recurrent *Clostridium difficile* infection [63]. Male NOD mice have a lower incidence of T1D than female NOD mice. Interestingly, male microbiota transfer to very young NOD female mice substantially protects against the development of T1D by increasing testosterone as well as metabolomic changes, reducing

islet cell inflammation and autoantibody levels [64]. Probiotics can boost immune responses, although their effects are transient and not particularly robust [65]. The commensal *Faecalibacterium prausnitzii* is associated with possible anti-inflammatory effects in Crohn's disease [66], and a mixture of clostridial species provides protection against experimental colitis and suppresses IgE responses [48]. However, the responsible factors derived from these commensal organisms are not known. Given the numerous species inhabiting the human gut [3], there is tremendous potential for the discovery of other commensal microbes and antigens that, like *B. fragilis* PSA, prime the immune system and may serve as therapeutic agents in immune diseases.

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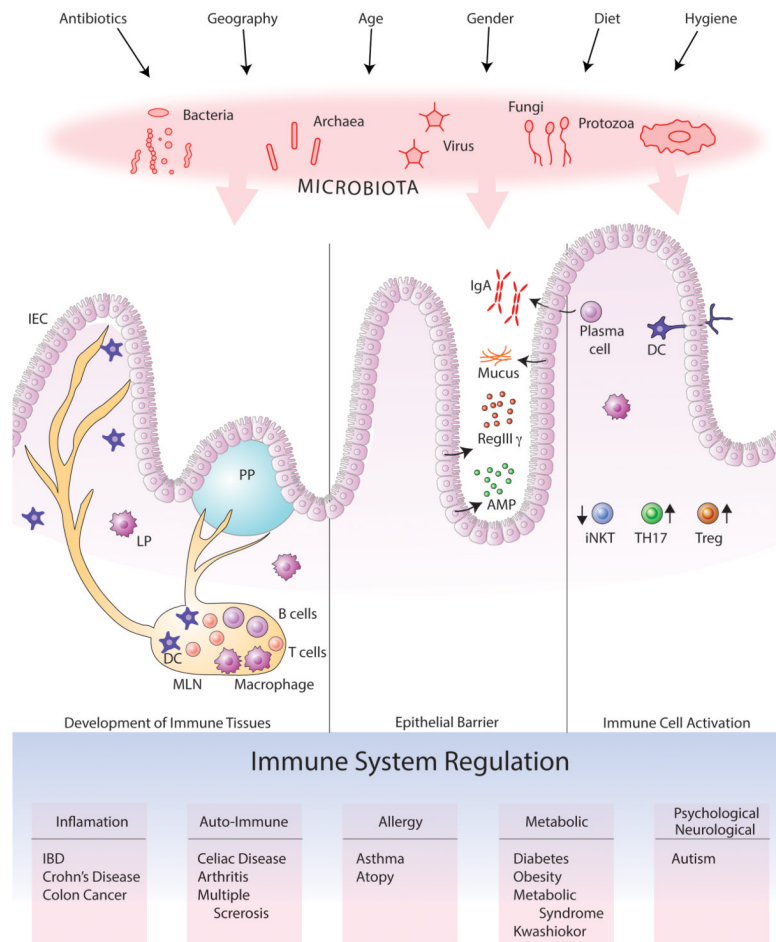
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### Highlights

- Composition of microbiota may affect host physiology
- Studies show the role of early microbial exposure in reducing disease susceptibility
- Commensal bacteria offer significant potential in therapy for a range of diseases
- Discovery of new commensal antigens to be used as therapeutic agents is imminent



**Figure 1. Commensal microorganisms shape the host immunity by multiple mechanisms**  
Mammals coevolved with their commensals, comprised of mostly bacteria but also include viruses, fungi, archaea and protozoa. Several factors such as hygienic conditions, antibiotic use, diet, sex and age of the host determines the composition of the microbiota, which in turn interacts with host tissues to orchestrate a finely tuned immune system. A healthy microbiota provides immunomodulatory signals for the development of immune tissues, secretion of antimicrobial molecules by the epithelial barrier and activation of immune cells. Any disturbance in these interactions results in an imbalanced immune system with consequent susceptibility to various diseases.