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INVITED REVIEW

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# Regulation of immune responses to food by commensal microbes

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## Summary

The increasing prevalence of immune-mediated non-communicable chronic diseases, such as food allergies, has prompted a deeper investigation into the role of the gut microbiome in modulating immune responses. Here, we explore the complex interactions between commensal microbes and the host immune system, highlighting the critical role of gut bacteria in maintaining immune homeostasis. We examine how modern lifestyle practices and environmental factors have disrupted co-evolved host–microbe interactions and discuss how changes in microbiome composition impact epithelial barrier function, responses to food allergens, and susceptibility to allergic diseases. Finally, we examine the potential of bioengineered microbiome-based therapies, and live biotherapeutic products, for reestablishing immune homeostasis to prevent or treat food allergies.

**KEYWORDS**
butyrate, commensal bacteria, food allergy, live biotherapeutic products, microbiome

## 1 | INTRODUCTION

There has been a generational surge in immune-mediated non-communicable chronic diseases including food allergies, obesity, diabetes, asthma, autism, and inflammatory bowel diseases (among others). The increasing prevalence of food allergies has been especially striking, in part, because allergic responses to certain foods, like peanuts, can be deadly.[1] Reactions are unpredictable and can range from urticaria to life-threatening anaphylaxis. Any food can elicit an allergic response, but nine foods are responsible for the most reactions: milk, eggs, peanuts, tree nuts, soybeans, wheat, fish, crustacean shellfish, and sesame.[2] The dominant allergens for each of these foods have been characterized; what they seem to share is an ability to resist degradation by gut proteolytic enzymes.[3,4] Food allergies typically present in early life and were once outgrown by school age. However, in recent years, many food allergies continue (or first appear) in adulthood. Initially reported in the United States, Europe and Australia, a rising disease incidence is now noted worldwide.[1,5] In the United States, an estimated 32 million children and adults currently suffer from food allergies.[5,6] Like most immune-mediated diseases, there is evidence for genetic susceptibility to food allergies but genetics alone cannot explain a marked generational increase in disease prevalence.[7] We, and others, have linked the rise of non-communicable chronic diseases in industrialized societies to lifestyle factors which lead to changes in the composition and function of the microbiome, that is, the resident commensal microbes which colonize the skin and all mucosal surfaces.[8–12]

## 2 | DEFINING THE MICROBIOME

Many (if not most) multicellular organisms harbor resident symbiotic microbes.[13] Some of these host–microbe relationships are commensal (from Latin: sharing a table), benefiting one species but affording neither help nor harm to the other, but many are mutualistic, providing important physiological benefits to both organisms. Although this review will focus on intestinal bacteria, the human microbiome includes bacteriophage, fungi, viruses, archaea and, in the developing world protozoa and helminths, that colonize multiple body sites.[12] A preponderance of these microbes resides in the anaerobic environment of the lower gut in numbers that are at least equal to the somatic cells of their host.[14,15]

The history of gut microbiome research can be traced back to Louis Pasteur and the emergence of the field of microbiology in the mid-nineteenth century.[16] Studies as far back as 100 years ago linked the gut microbiome to vitamin production and showed that gut microbes can provision rodent hosts with essential vitamins.[17] Seminal reports from the 1950s demonstrated that fecal material from a healthy individual could be transplanted to patients following antibiotic-mediated microbiome depletion to confer resistance to bacterial pathogens.[18,19] Subsequent work characterized the composition of the gut microbiome[20] and identified its roles in drug metabolism[21] and digestion.[22] While insight into many key attributes of the gut microbiome had therefore emerged by 1980, progress in the field largely languished through the 1990s. Several factors led to a dramatic increase in interest in the gut microbiome in the early 2000s. One key development was the establishment of culture-independent DNA sequencing technologies and the creation of bioinformatic tools that enabled the characterization of bacterial and archaeal communities via sequencing of their highly conserved 16S ribosomal RNA (16S rRNA) gene.[23,24] Application of these tools showed that hundreds of site-specific resident bacteria occupy the skin and mucosal surfaces and display a remarkable degree of genetic diversity.[25,26] Around the same time, several landmark studies demonstrated substantial differences in microbiome composition across subjects and linked these compositional differences to complex host phenotypes.[27–29] The combination of an accessible research toolkit and evidence of the microbiome's involvement in the regulation of health and disease laid the foundation for a dramatic expansion of studies in the field. Microbiome research grew rapidly from the late 2000s through the early 2010s, with much of the research in this period applying 16S rRNA analysis to identify changes in microbiome composition that correlated with various host states. Since then, the methodological tools available have greatly improved and researchers have begun to develop more mechanistic insight into how the microbiome modulates host phenotypes. Studies that use 16S rRNA analysis, which only generates a crude genus-level approximation of the composition of the bacterial and archaeal microbiome, have increasingly been replaced by metagenomic approaches that comprehensively sequence available genetic material. Metagenomics analyses enable strain-level classification of prokaryotes, eukaryotes, and viruses and provide direct information about the genetic content of microbiomes. Maturation of the field has also led to the advancement of metabolomics methods to track microbial molecules[30] and the establishment of manipulable humanized animal models of the gut microbiome.[31] The ability to generate and test hypotheses about molecular factors responsible for microbiome-mediated host phenotypes has thus advanced considerably in recent years.

The gut microbiome may be best understood as an integral component of the digestive organ. Appreciating this primary function is critical for understanding the host–microbe co-evolution that gave rise to the microbiome and the specific attributes that emerged. Thousands of enzymes are required to break down chemically diverse dietary components, including variable linkages found within complex polysaccharides.[32] Encoding the enzymes required to digest these compounds would require the host to dedicate an impractical fraction of its genome to this process. By making the large intestine a near-perfect environment for microbial fermentation, evolution arrived at a clever solution to the digestive challenge posed by the chemical complexity in food. After common and chemically simple dietary components, such as proteins, fats, and carbohydrates, are digested and absorbed in the small intestines, dietary fiber (consisting of plant polysaccharides and other undigested material) passes into the large intestines. The hundreds of species of bacteria that colonize the large intestines encode thousands of enzymes that allow them to digest the remaining contents.[32,33] The impressive digestive capacity of the gut bacterial microbiome is illustrated by the observation that gut bacteria collectively encode approximately 1000-fold more polysaccharide-degrading digestive enzymes than their human hosts.[34]

The anaerobic properties of the lower gastrointestinal tract reflect another evolutionary ingenuity essential for gut bacteria's role in digestion. The absence of oxygen in the lower gastrointestinal tract necessitates that bacteria forgo respiration in favor of fermentative metabolisms. Consequently, the collective activity of gut bacteria converts chemically diverse fiber constituents into fermentation products. The predominant fermentation products generated by this complex bacterial community comprise the short-chain fatty acids (SCFAs) acetate, butyrate, and propionate (Figure 1). These SCFAs are absorbed by the large intestines and used as an energy supply.[35] The percent of dietary calories derived from bacterial SCFAs varies between animals, but is estimated to increase the energy extracted from the diet by 5%–10% in humans.[36] In addition to being key digestive products for host energy assimilation, SCFAs modulate multiple host pathways and have been linked to numerous microbiome-mediated phenotypes. The fermentative pathways that generate SCFAs are differentially distributed across gut bacteria. Acetate is broadly produced by many taxa, while butyrate and propionate arise from a narrower subset of gut bacteria.[37] Butyrate is principally produced by Gram-positive bacteria (particularly the Lachnospiraceae family of Clostridia), whereas propionate is mainly produced by Gram-negative bacteria (including Akkermansia, Bacteroidales, and Enterobacteriaceae).[38,39] Intestinal SCFAs therefore serve as key

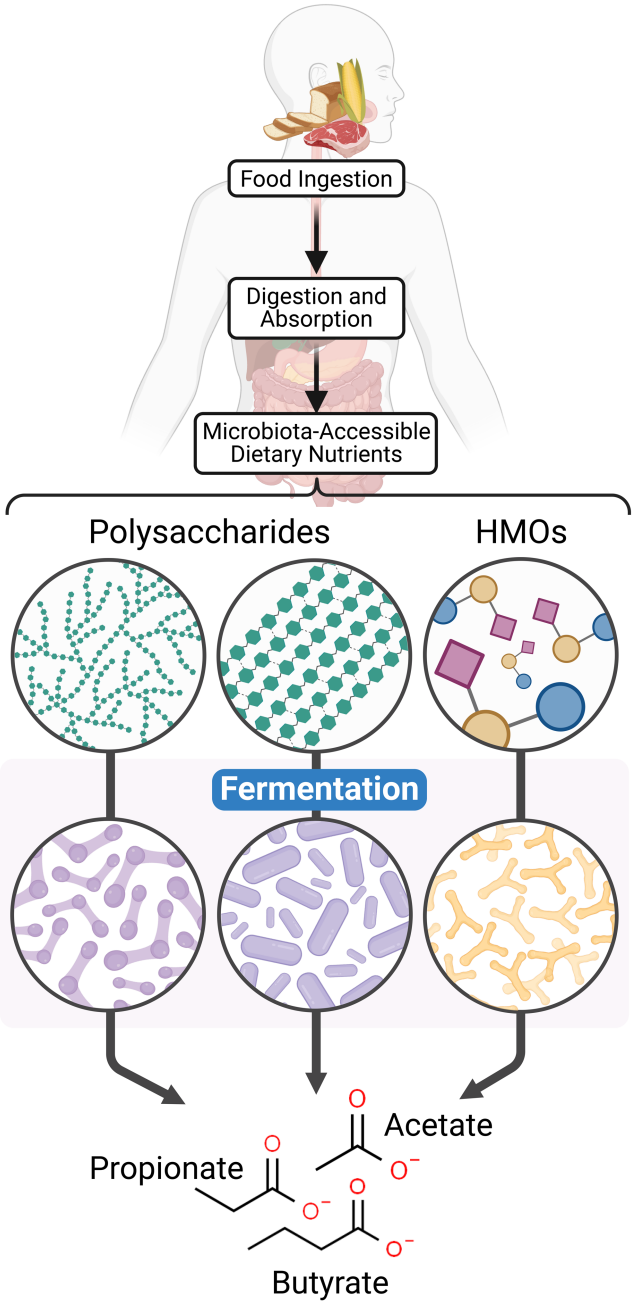


**FIGURE 1** Schematic depiction of the gut microbiome's digestive function. Undigested dietary components, including complex polysaccharides and human milk oligosaccharides (HMOs), are fermented by distinct members of the gut microbiome. Absorption of microbial fermentation products, including acetate, propionate, and butyrate, in the lower gastrointestinal tract increases digestive efficiency.

markers of the composition and activity of the gut bacterial microbiome. Perhaps related to the gut microbiome's digestive role, the lower gastrointestinal tract is extremely amenable to microbial colonization. The host's diet determines the nature of the undigested material that reaches the lower gastrointestinal tract, and consequently, the type of degradative activity performed by gut microbes. The permissiveness of the lower gastrointestinal tract to microbial colonization enables the microbiome to adapt to a near-limitless number of potential host diets. If existing microbes cannot ferment a particular dietary component, this untapped resource represents a potential exclusive microbial energy source. This, in turn, favors colonization by new microbes that possess the capability to ferment it. The composition of the gut microbiome is thus tailored to maximize collective fermentative output from any given diet. In addition to facilitating adaptations that promote microbiome activity, the permissibility of the lower gastrointestinal tract to microbial colonization means that the host does not discriminate between microbes that are comparably adapted for life in the gut. Consequently, stochastic or subtle events that lead to the presence of a particular microbe within a microbiome result in individualized microbiomes that collectively generate population-level variability in composition.

Differences in community composition and/or activity are fundamental drivers of all microbiome-mediated host phenotypes. The factors influencing differences in microbiome composition are not fully understood but can relate to distinctions in microbiome acquisition and development. The human fetus is sterile, but microbes are immediately encountered upon birth.[40–42] Mode of birth is therefore important for determining the infant's founder microbiome. Vaginally delivered babies are colonized by founder bacteria from their mother's vaginal canal and fecal stream during birth, resulting in the vertical transmission of microbial species across generations. Babies born by cesarean section were originally reported to acquire their founder bacteria from the skin of the mother, another person in the delivery room and even the hospital setting itself.[43–46] More recent work shows that transmission of microbes from mother to child occurs across multiple body sites during the first month of life and may be able to compensate for the loss of exposure to maternal vaginal/fecal microbes in babies born by cesarean section.[47–49] In support of this idea, transfer of the vaginal microbiota (vaginal seeding) was only marginally successful in altering the founder microbiome of cesarean section babies.[50] Fecal transplant was more successful and no differences in the microbiomes of vaginally and cesarean section-delivered babies were detected after transfer of the mother's fecal microbiome to cesarean section babies.[51]

Following birth, multiple factors result in a gradual shift in the composition of the microbiome with breastfeeding playing a central early role. Human milk oligosaccharides (HMOs) within breastmilk strongly modulate the microbiome through a mechanism that likely reflects evidence of a host–microbe co-evolutionary history. The human genome does not encode the enzymes required to digest HMOs, and consequently, this energy-rich component of the milk reaches the lower gastrointestinal tract undigested.[52] Populations of bacteria, namely, Bifidobacteria, are specially adapted to digest HMOs and produce metabolites which promote the development of the immune system and prevent inflammation.[53] Given this critical function, it is perhaps not surprising that *Bifidobacterium* spp. are consistently vertically transmitted from mother to child regardless of delivery mode.[54] Bifidobacterial strain diversification

correlates with length of breastfeeding which, by 1 year of age, may have a more long-lasting impact on the composition of the infant microbiota than mode of birth.[54] Although there are some reports of a breast milk microbiome, it is not clear how microbes could translocate from the mother's gut to the mammary glands. Other studies suggest that microbes detected in breast milk are most likely derived from the mother's skin or the baby's mouth during feeding.[49,55,56]

With weaning and the introduction of solid food, the infant microbiome continues to diversify in an ordered succession.[57–61] Early colonizers change global properties like the redox potential of the gut,[62] and this enables colonization of specialized microbes that are specifically adapted for conditions present in the mature gut microbial ecosystem.[63] The origin of microbes that colonize the gut after birth is not fully understood but seems to come from multiple different environmental sources including soil, plants, and animals. Studies of Amish and Hutterite populations in the United States showed that children from similar genetic backgrounds who grew up on traditional farms, in close association with livestock, had more diverse gut microbiomes than those living in mechanized farms.[64] In urban settings, microbes are exchanged in indoor (built) environments, with cohabitants sharing many aspects of microbiome community structure.[65–67] The extent and nature of exposure to environmental sources of microbes is thus an important factor in microbiome development. Chance colonization events and lifestyle factors are both important in shaping the composition of the gut microbiome. Longitudinal profiling studies confirm that each individual's established microbiome is unique, analogous to a fingerprint.[68] The microbial community varies in response to dietary changes or illness but tends to return to a set baseline.

## 3 | LIFESTYLE FACTORS IMPACT THE ACQUISITION AND DIVERSITY OF THE MICROBIOME

Coincident with the rise in non-communicable chronic diseases, various lifestyle factors of industrialized societies have collectively resulted in changes in the human microbiome. As discussed above, diet is a major driver of diversification of the microbiome. Throughout history, human societies consumed much larger quantities of plant-derived dietary fiber than are present in the 21st century Western diet.[69] These microbiota accessible carbohydrates play a critical role in shaping the composition, and function, of the microbiome.[10,11,70] Immigration from a non-Western country to the United States, and consumption of a Western diet, is associated with a rapid loss of gut microbiome diversity.[71] Even short-term interventions with a high-fiber or fermented foods diet can increase gut microbial diversity and reduce signs of immune inflammation in the peripheral blood.[72] Other features of modern societies also impact the gut microbiome. Vaccine-induced reductions in infectious disease, improvements in sanitation, and the elimination of previously common enteropathogens, like helminthic parasites, contribute to the reduced diversity of the industrialized gut microbiome.[73–76] Urbanization and the departure from a traditional farming lifestyle is associated with loss of microbiome diversity.[64,77,78] Numerous products of industrialization may also contribute to observed microbiome changes. Emerging data suggest that environmental chemicals, including common household products and food additives can alter the microbiome. For example, detergents commonly added to soaps and toothpastes change the composition of the esophageal microbiome and modulate epithelial barrier function.[79] Dietary emulsifiers and even artificial sweeteners have been associated with alterations in the gut microbiome[80–82] (Figure 2).

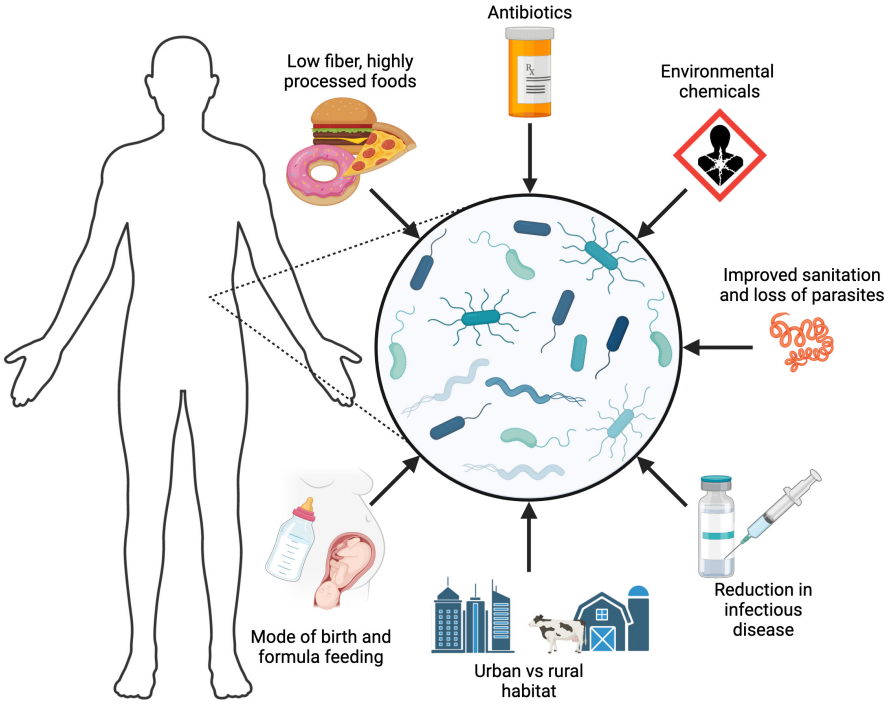


FIGURE 2 Twenty-first-century lifestyle factors disrupt co-evolved host–microbe relationships to reduce commensal microbial diversity. These include mis or over-use of antibiotics, consumption of a low fiber, highly processed diet, cesarean birth, and formula feeding, urban habitats, reduction in infectious disease through vaccination, elimination of previously common parasites through improvements in sanitation and increasing exposure to cytotoxic environmental chemicals. Collectively, depletion of symbiotic host protective microbes contributes to the increasing prevalence of non-communicable chronic diseases, including food allergy (adapted from ref. 9).

Antibiotic use and misuse are the greatest modifiers of the microbiome.[44,83,84] Antibiotics have, of course, been lifesaving for the treatment of many infectious diseases. However, most have broad-specificities and deplete the bacterial microbiome as collateral damage.[85–87] Many resident bacterial taxa recover, but persistent disruption of both the composition and function of the microbiota is also common and associated with non-communicable chronic diseases.[88] Antibiotic administration in early life is particularly damaging to the developing microbiome.[44,83,84] For example, repetitive ear infections in infants are typically treated with the antibiotic amoxicillin-clavulanic acid.[89] Recent work testing the effect of amoxicillin-clavulanic acid treatment showed that neonatally treated mice exhibited long-term depletion of key microbial metabolites, dysregulated airway epithelial function, and exacerbated responses to sensitization with house dust mites, despite an apparent rapid recovery in gut microbiota composition.[90] In humans, antibiotic treatment in early life also correlates with the increasing prevalence of asthma.[91] Murine model studies showed that administration of subtherapeutic doses of antibiotics in early life alters hormone levels and induces a metabolic syndrome that leads to increased adiposity.[92] Widespread environmental exposures to antibiotics and antimicrobials may be another factor contributing to observed microbiome changes. Low doses of antibiotics were utilized for more than 50 years in livestock production to increase weight gain,[93] until concerns over antibiotic resistance led the FDA to ban non-therapeutic uses of antibiotics in livestock in 2017.[94] Triclosan, an antimicrobial impregnated in thousands of consumer products from toothpastes to clothes and toys, is another source of environmental exposure. The detection of triclosan in urine is associated with changes in gut microbiome composition,[95] and correlated with an increased risk of both inhalant and food allergies.[96]

## 4 | COMMENSAL MICROBES REGULATE IMMUNE RESPONSES TO FOOD

The gut-associated lymphoid tissue faces an enormous challenge in distinguishing the broad array of commensal microbes and innocuous dietary antigens from potential pathogens and mounting an appropriate response to each.[9] Not surprisingly, the physiological default response to dietary antigens is systemic nonresponsiveness.[97] Often referred to as oral tolerance, this nonresponsiveness can be modeled experimentally by measuring the response to peripheral immunization with antigen plus adjuvant weeks after intragastric gavage of the same antigen.[98] Because the mechanisms regulating a failure to respond are inherently difficult to study, in early work we examined whether tolerance to a dietary antigen was altered in the context of a local, mucosal infection. We chose infection with the natural murine helminthic parasite, *Heligmosoides polygyrus*.[99] *H. polygyrus* elicits a pronounced Th2-biased immune response, including parasite specific polyclonal IgG1/IgE antibodies. We found that tolerance for a Th1-dependent cytokine or antibody response to ovalbumin (OVA) was maintained, but Th2 responses to OVA were primed, in *H. polygyrus*-infected mice.[100,101] In addition to creating a Th2-biased mucosal cytokine environment, helminth infection acted as an adjuvant for the response to a dietary antigen by upregulating costimulatory molecules on mucosal dendritic cells (DC) and promoting the proliferation of antigen-specific T cells.[101] The impact of helminth infection on immune responses to food was revisited recently in a preprint report employing state-of-the-art Labeling Immune Partnerships by SorTagging Intercellular Contacts (LIPSTIC) detection together with single-cell transcriptomic methodologies.[102] Mucida and colleagues found that the ability of specific subsets of DC to induce regulatory T cells (Tregs) in response to orally administered antigens was partially abrogated in helminth-infected mice, confirming the influence of helminth infection on the immune response to a food. In a later study, we were surprised to find that helminth-infected mice were protected from an anaphylactic response to food induced by sensitization with peanut plus the mucosal adjuvant cholera toxin.[103] Helminth-mediated protection was IL-10-dependent, in keeping with studies which showed that, despite sensitization, African children in helminth endemic areas had high levels of circulating IL-10 and little evidence of atopy.[104] Endemic enteric helminths in the developing world have co-evolved with gut bacterial inhabitants and the composition of the fecal bacterial microbiota is altered in individuals colonized with helminths when compared to non-infected individuals.[105] Helminth infection can therefore modify host immunity both directly and through its effects on the microbiome.

Inspired by a newly emerging consensus that the intestinal immune hyperreactivity in inflammatory bowel disease (IBD) was not primarily autoreactive but was instead directed against (and controlled by) resident intestinal bacteria,[106,107] we asked whether intestinal bacteria also regulate the response to the other major luminal constituent—food. We showed that depletion of intestinal bacteria by neonatal administration of oral broad spectrum antibiotics increased susceptibility to allergic sensitization to peanut.[108] We later demonstrated that the antibiotic-induced reduction in bacterial diversity led to impaired epithelial barrier function.[109] We used gnotobiotic models to examine the barrier-protective capacity of various bacterial populations. We found that administration of a consortium of mucus-associated spore-forming bacteria from the Clostridia class induced an IL-22-dependent epithelial barrier-protective response, which decreased the concentration of intragastrically administered peanut protein detectable in serum and prevented allergic sensitization to food.[109] Earlier work had shown that presentation of dietary antigen in gut-draining mesenteric lymph nodes, rich in TGF-β and the vitamin A metabolite retinoic acid, induced the peripheral conversion of naive $CD4^+$ T cells to dietary antigen-specific $Foxp3^+$ regulatory T cells (Tregs).[110–112] Subsequent reports demonstrated that the induction of oral tolerance was a multistep process, which required that these Tregs acquire homing receptors which allowed them to migrate to, and expand in, the intestinal lamina propria.[113] Studies in antigen and microbe-free mice confirmed that $Foxp3^+$Tregs in the small intestinal lamina propria were largely dietary antigen-specific while

those in the colon had specificity for intestinal bacteria.[114] We proposed a Barrier Regulation Hypothesis of allergic sensitization which suggested that, in addition to the induction of food antigen-specific Foxp3$^+$ Tregs, a bacteria-induced barrier-protective response was required to maintain epithelial barrier integrity and induce tolerance to dietary antigens.[115] We showed that bacteria in the Clostridia class are one taxon which mediate this barrier-protective response. They do so by inducing type 3 innate lymphoid cells (ILC3) to secrete IL-22, which stimulates epithelial production of mucus and other mediators which, together, block access of dietary antigen to the systemic circulation. Other work showed that depletion of barrier-protective taxa in mice maintained on a fiber-free diet resulted in the expansion of the mucin degrading specialist *Akkermansia mucinophila*, thinning of the mucus layer, impaired epithelial barrier function, and enhanced allergic responses to food.[116]

Remarkably, a single-cell-layered epithelium is all that separates trillions of microbial inhabitants from the underlying intestinal lamina propria and the activation of immune effector cells in the gut-associated lymphoid tissue.[117] Most cells in the small intestinal epithelium are absorptive enterocytes, in keeping with this tissue's central role in the processing and digestion of dietary nutrients. A small fraction of epithelial cells belongs to the secretory lineages, composed of several specialized cell types, which help to maintain barrier integrity: enteroendocrine cells, goblet cells, tuft cells, and Paneth cells.[118] Enteroendocrine cells secrete hormones that regulate digestion, absorption of dietary nutrients, and gastrointestinal motility.[119] Tuft cells (discussed below) "sense" the luminal contents.[120] Mucus produced by goblet cells forms a physical barrier at the epithelial surface.[121] Paneth cells are a prominent source of antimicrobial peptides (AMPs), natural antibiotics that maintain the sterility of the villus crypt and regulate the composition of the microbiota.[122] In addition to these components of the physical epithelial barrier, the maturation of the nascent immune system is intimately intertwined with neonatal colonization by commensal bacteria.[115,123,124] In mice, a distinctive, microbiota-driven weaning reaction occurs during the transition from mother's milk to solid food. This initial host reaction to its resident microbiota is central to the development of intestinal immune homeostasis; the absence of the weaning reaction leads to increased susceptibility to pathological responses to luminal antigens (food allergies and colitis) later in life.[125] A physiological decrease in the concentration of epidermal growth factor receptor ligands in the mother's breast milk during the second week of life opens goblet cell associated passages (GAPs) and allows for translocation of microbial antigens to the lamina propria.[126] Weaning is accompanied by a 100-fold increase in both the relative abundance and numbers of Clostridia and a smaller increase in Bacteroidia in the terminal ileum.[125] Innate immune signals elicited by these changes trigger a transient spike in TNF-α and IFN-γ production by T cells in the terminal ileum. In the presence of both bacterial SCFAs produced by the new colonizers and retinoic acid, microbial antigens presented by CD103$^+$ DC induce the conversion of naïve T cells to a unique population of bacteria-induced Foxp3$^+$RORγt$^+$ Tregs critical to intestinal homeostasis.[125,127] Recent work has suggested that it is not DC, but a novel lineage of RORγt$^+$ antigen presenting cells (APC) called Thetis Cells, (with shared transcriptional features of thymic medullary epithelial cells and DC) that mediates tolerance to the gut microbiota.[128] A preprint report suggests that a subset of Thetis Cells (TC IV) is required to induce food-specific Tregs and oral tolerance in early life.[129]

The changes in gene expression induced between weeks two and three (as the weaning reaction develops) reflect the differentiation of Paneth and goblet cells and increased production of AMPs and mucus.[125] Work from our laboratory also supports a critical role for commensal Clostridia in the establishment of epithelial barrier integrity. We found that commensal Clostridial flagellin and indoles signal through TLR5 and the Aryl Hydrocarbon Receptor (AhR), respectively, to elicit an IL-22-dependent gut barrier-protective response.[130] Some Clostridial taxa are motile and bear flagella, a ligand for TLR5, or produce tryptophan metabolites (including indoles), which are ligands for the AhR. We found that lysates and flagella from a consortium of Clostridia induced IL-22 secretion from ileal explants from wild-type mice but not from mice deficient in TLR5 or MyD88 either globally or conditionally in CD11c$^+$ APC. AhR signaling in RORγt$^+$ ILC3 was necessary for flagellin-mediated induction of IL-22. Mice with an AhR deficiency in RORγt$^+$ cells exhibited increased intestinal permeability to luminal antigens, and enhanced susceptibility to an allergic response to food. Our data therefore suggest that Clostridial products regulate a continuum of responses, that begins with the weaning reaction, and results ultimately in a barrier-protective response (Figure 3).

To begin to translate our mouse model work to human disease, we examined the composition of the fecal microbiota in a demographically matched Italian cohort of healthy infants and infants with cow's milk allergy (CMA).[131] We found that taxa typically detected in healthy 4-month-old infants including Lactobacillales, Bifidobacteriales, and Enterobacteriales were all depleted in CMA infants, who instead exhibited an accelerated maturation of their microbiota to a community composition more similar to what is found in adults. Treatment with an extensively hydrolyzed casein formula supplemented with *Lactobacillus rhamnosus GG* was associated with enhanced acquisition of tolerance to cow's milk and increased concentrations of fecal butyrate.[131] We then went on to demonstrate a causal role for bacteria present in the healthy infant microbiota in protection against CMA.[132] We developed a gnotobiotic model of CMA in which we transferred feces from four healthy and four CMA 6-month-old infants to germ free (GF) mice.[132] Groups of GF mice and mice colonized with either healthy or CMA infant feces were sensitized with the cow's milk protein β-lactoglobulin (BLG) and the mucosal adjuvant cholera toxin. Consistent with previous reports,[109,133] GF mice, devoid of any bacterial colonization, were highly susceptible to an anaphylactic response to food, as evidenced by a drop in core body temperature and production of BLG-specific IgE and IgG. There was also a significant reduction in core body temperature in mice colonized with fecal samples from each of the four CMA donors in response to BLG challenge. Sensitized CMA-colonized mice

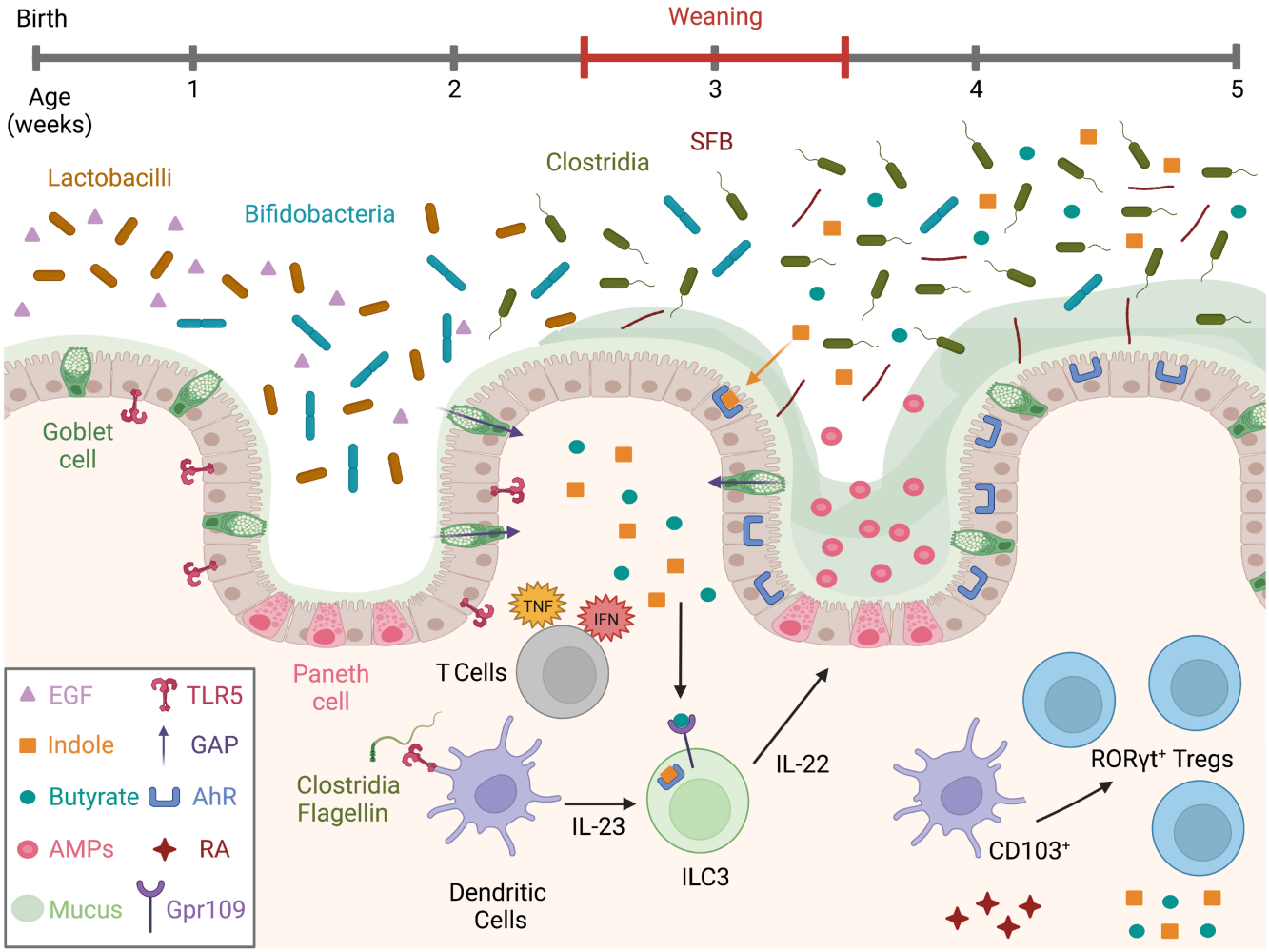


**FIGURE 3** Commensal Clostridia are key mediators of both the weaning reaction and the establishment of homeostasis in the intestinal mucosa. Lactobacilli and Bifidobacteria are dominant intestinal taxa shortly after birth. During this time, suckling mice also receive relatively high amounts of epidermal growth factor (EGF) receptor ligands from breast milk. As breast milk EGF levels are reduced goblet cell-associated passages (GAPs) open to allow microbial antigens to gain access to the lamina propria (LP). Commensal Clostridia expand dramatically with exposure to solid food at weaning. The weaning reaction is characterized by a short-lived increase in TNF-α and IFN-γ and the presence of new products from the changing microbiome in the intestinal LP. These include tryptophan metabolites which interact with the Aryl Hydrocarbon Receptor (AhR) on various cell types, particularly type 3 innate lymphoid cells (ILC3). Some Clostridia are motile-their flagellin signals through TLR5 and activates dendritic cells (DC) to produce IL-23 which induces downstream secretion of IL-22 from ILC3. In addition, short-chain fatty acids such as butyrate interact with GPR109 on ILC3 to induce IL-22. Microbial antigens displayed by CD103$^+$ DC in the presence of retinoic acid (RA) and bacterial metabolites induce the conversion of naïve T cells into Foxp3$^+$RORγt$^+$ regulatory T cells (Tregs). Between weeks 2 and 3, significant changes in gene expression contributeto the differentiation of crypts and increased production of mucus and antimicrobial peptides (AMPs) from goblet and Paneth cells respectively. The interactions of commensal Clostridia with their host therefore occur along a continuum, beginning at weaning, that ultimately leads to a bacteria-induced epithelial barrier-protective response critical to mucosal homeostasis.

produced markedly higher serum concentrations of BLG-specific IgE, IgG1, and mouse mast cell protease 1 (mMCPT-1) when compared to healthy-colonized mice. Strikingly, all of the mice that received healthy infant feces were protected from an anaphylactic response to BLG challenge; their core body temperature was significantly different from that measured in GF or CMA-colonized mice. The integration of differentially abundant taxa present in the healthy and CMA microbiotas with the changes in ileal gene expression each induced upon colonization of GF mice identified a single butyrate-producing Clostridial species, *Anaerostipes caccae* selectively enriched in mice colonized with the healthy infants' microbiota.[132] Mice monocolonized with *A. caccae* mimicked the effects of the healthy microbiota in protection against an anaphylactic response to food.[132] Later in the same year, Chatila and colleagues.[134] published similar findings suggesting that, in addition to Clostridia, other taxa can also protect against food allergy and that they do so by inducing Foxp3$^+$RORγt$^+$ Tregs in the mesenteric lymph node in a Treg intrinsic MyD88 dependent fashion. Foxp3$^+$RORγt$^+$ Tregs were required for microbiota-mediated protection in murine models of food allergy and were reduced in the peripheral blood of food allergic patients.[134] The MyD88-dependent ligand was not identified.

To broaden the fecal microbial signatures to a larger, more diverse group, we performed taxonomic and metabolomic analyses of samples from a cohort of twin pairs concordant and discordant for food allergy. We found that most of the bacteria differentially abundant between healthy and allergic twins were in the Clostridia class; the marked age range of the twins studied (6 months to 70 years) supported our premise that early-life depletion of barrier-protective Clostridia was maintained with aging and was associated with allergic disease.[135] The small sample size examined was a limitation of our study, but an earlier report from the Consortium for Food Allergy Research (CoFAR) corroborated our findings in a much larger cohort.[136] CoFAR collected fecal samples from 226 children enrolled in an observational study of milk allergy.[136] They reported that certain taxa within the Clostridia were enriched between ages 3–6 months in children with CMA whose disease had resolved by 8 years of age when compared to those with persistent disease. Blautia, a prominent butyrate producer was selectively enriched in tolerant infants in both our initial report and the CoFAR study.[131,136] Differential abundances of various other taxa, without a unifying discernible signature, have been reported in several other studies comparing fecal samples from patients with food allergies to non-allergic controls.[137–139]

Although we have emphasized an allergy protective role for the microbiota, some evidence also suggests that populations of intestinal bacteria can promote food allergy.[140] The microbiomes of infants from the Italian pediatric cow's milk allergy cohort described above were enriched for genes involved in the biosynthesis of the pro-inflammatory TLR4 ligand lipopolysaccharide.[140,141] Intestinal microbial metabolites, which promote type II immunity, are less well studied than those which are protective. However, several groups have shown that microbially produced succinate induces type II immunity by binding to its receptor, SucnR1, on tuft cells to trigger the secretion of the epithelial alarmin IL-25.[142–147] Although others have speculated that this pathway may be involved in the development of food allergy,[148] this question has yet to be experimentally interrogated. Specific helminths and protists induce SucnR1-mediated type II immunity; these organisms are rare in industrialized societies and therefore unlikely sources of allergy-relevant succinate. Some bacteria have been implicated in the induction of SucnR1-mediated type II immunity, but the broader factors responsible for bacterially derived succinate accumulation are not fully understood.[145,147] *Phascolarctobacterium faecium* is known to be among the few taxa of succinate-consuming specialists, which metabolize succinate to propionate.[149–152] Interestingly, in our study of the gut microbiomes of twins concordant and discordant for food allergy, we found that *P. faecium* was one of only two taxa associated with protection from food allergy.[135]

## 5 | DEVELOPMENT OF MICROBIOME-MODULATING THERAPEUTICS FOR FOOD ALLERGY

Probiotics are live microorganisms that are intended to confer health benefits when consumed.[153] Conventional probiotic formulations typically include aerotolerant environmental Lactobacilli or Bifidobacteria strains that inefficiently colonize the gastrointestinal tract. These probiotics have been studied for many years and have shown limited efficacy for the treatment of allergic disease, as reviewed elsewhere.[154] We will focus here on "next generation" live biotherapeutic products (LBPs), which contain anaerobic gut microbes that colonize the gastrointestinal tract and directly change microbiome composition. Driven initially by the successful treatment of *C. difficile* colitis by transfer of donor feces,[155] there has been substantial academic and commercial interest in the development of LBPs to treat a variety of diseases. The use of donor samples has, however, been impossible to standardize given that every individual's microbiome is unique to the strain level and that different strains of a single species can have varied functional activities.[156,157] Recent clinical trials have shown that the transfer of selected bacterial consortia (typically dominated by Clostridia) appears to be safe, but engraftment comes with some trade-offs; pre-treatment of the recipient with antibiotics is often required, presumably to open a niche.[158,159] Moreover, introduction of new taxa can displace others, like the health-associated bacterial strain *Faecalibacterium prausnitzii*.[159] The consequences of this displacement are not known. Beyond the initial success with *C. difficile* colitis, the efficacy of live biotherapeutics in the treatment of other diseases has not been demonstrated in clinical trials to date, although many are in progress. Of relevance to this review, the safety and efficacy of oral–fecal microbial transplantation therapy (with antibiotic pre-treatment) is currently being investigated in an interventional trial for peanut allergy in a small group of teenagers.[160]

The difficulties inherent in transferring live anaerobic bacteria suggested that treatment with a product of these bacteria might be an alternative approach. As discussed above, SCFAs are prominent microbial metabolites with well-documented immunoregulatory properties. Bacteria in the Clostridia class are dominant producers of butyrate. In keeping with its role as a vital cellular energy source for the intestinal epithelium, butyrate utilizes several largely non-redundant mechanisms of action to maintain mucosal barrier integrity. These can be grouped into three broad categories: (1) signaling through G protein-coupled receptors (GPRs), (2) regulation of gene expression, and (3) modification of immunometabolism. Cell surface G protein-coupled receptors GPR43 (Ffar2), GPR41 (Ffar3), and GPR109a, expressed on both the intestinal epithelium and cells of the innate immune system (neutrophils, DC, macrophages, and ILC), regulate mucosal immunity to pathogens.[161,162] Binding to cell surface GPR41/43 signals intracellularly through the PI3K-Akt signaling pathway to promote cellular activation and proliferation. Transcriptional activation is suppressed by histone deacetylation (HDAC), which induces a closed chromatin conformation. Butyrate acts as an HDAC inhibitor to epigenetically regulate gene expression.[161] HDAC inhibition by butyrate restrains pro-inflammatory cytokine expression in macrophages and DC[163,164] and suppresses mTOR activity in macrophages to "imprint" an antimicrobial program.[165] Butyrate also enhances acetylation of the Foxp3 locus and protein to promote the peripheral expansion of Foxp3$^{+}$Tregs.[163,166,167] Conversely

butyrate decreases acetylation at the promoter regions of the tyrosine kinases required for IgE-FcεR1-mediated mast cell degranulation.[168] SCFAs potentiate the effector function of Th1 and Th17 cells by increasing both protein acetylation (HDAC inhibition) and the activation of mTOR.[169] Regulation of cellular metabolism by SCFAs also aids in the differentiation of IgG- and IgA-secreting B cells to plasma cells.[170,171] Interestingly, SCFAs also suppress the production of IgE.[161,172]

Decreased production of butyrate, in particular, has been linked to susceptibility to allergic disease, especially in early life.[173–175] Metagenomic analysis of fecal samples from 3-month-old infants who exhibited allergic sensitization in early childhood revealed a reduced potential for carbohydrate degradation and decreased abundance of butyrate-producing taxa.[176] The protection against asthma and allergy afforded by a traditional farm lifestyle markedly correlated with the expansion of butyrate-producing taxa.[177] Conversely, murine model studies showed that antibiotic-mediated depletion of butyrate-producing taxa in early life dysregulated a ILC2-B1 B cell-IgE axis, leading to enhanced susceptibility to allergic lung inflammation.[178] Clinically, the use of butyrate has been restricted by its foul smell and taste and little evidence that orally administered butyrate can reach the lower gut where it is normally produced. To circumvent these limitations, we conjugated butyrate to block copolymers which form micelles with butyrate in their hydrophobic core.[179] We created neutral and negatively charged formulations which differentially released butyrate in distinct regions of the lower gut. The unpalatable taste and smell of butyrate were masked in both polymer formulations. To achieve prolonged elevated luminal concentrations of butyrate throughout the lower gut we created a 1:1 mixture of the two formulations and examined its efficacy in protecting against an anaphylactic response to food. Groups of neonatally antibiotic-treated mice were sensitized with peanut plus the mucosal adjuvant cholera toxin. After confirming that a uniform allergic response had been induced, groups of mice were intragastrically gavaged twice a day with the mixed micellar formulations of butyrate (ButM). All of the mice were challenged with peanut extract after 2 weeks of treatment with ButM. An anaphylactic drop in core body temperature, serum mMCPT-1, histamine, and PN-specific IgE were all significantly reduced in mice treated with ButM.[179] To examine whether delivery of butyrate to the lower gut was necessary for its efficacy, we did a head-to-head comparison of intragastric gavage of ButM or equivalent concentrations of sodium butyrate. Free sodium butyrate had no effect in protecting allergic mice from an anaphylactic response to allergen challenge and did not reduce serum peanut-specific IgE and IgG1 levels, while ButM was highly effective.[179] Fecal samples were collected before and after ButM treatment to examine the composition of the microbiota. We found that ButM treatment significantly increased the abundance of a major butyrate-producing taxon, *Clostridium* cluster XIVa. This was likely due to butyrate's ability to signal through the transcription factor PPAR-γ to shunt enterocyte metabolism toward β-oxidation, creating regions of localized hypoxia, which support the growth of obligate anaerobes.[180] ButM treatment therefore resulted in both increased luminal concentrations of butyrate and the expansion of populations of butyrate-producing Clostridia.

As already mentioned, we created a robust gnotobiotic model of cow's milk allergy (CMA) by transferring fecal samples from healthy and CMA infant donors to GF mice.[132] We found that mice colonized with the healthy infants' microbiota were protected from an allergic response to food while mice colonized with the CMA microbiota were susceptible.[132] Mono-colonization of germ-free mice with the butyrate-producing Clostridia *Anaerostipes caccae* mimicked the protective effect of the replete healthy infant microbiota and prevented an anaphylactic response to food.[132] We were interested in exploring *A. caccae* as a second therapeutic approach but were concerned that it would exhibit limited engraftment in microbially replete hosts. To create an ecological niche in the gut to maximize engraftment and butyrate production, we decided to co-deliver *A. caccae* with a prebiotic substrate, that is, as a synbiotic. *A. caccae* is a professional cross-feeder; it depends on other bacterial species to perform primary degradation of large polysaccharides and release small molecules such as lactate and acetate which *A. caccae* can then convert to butyrate.[181,182] We hypothesized that intentionally creating cross-feeding relationships between *A. caccae* and resident bacteria by administering a prebiotic would be an effective strategy to improve its efficacy. We isolated a novel strain of *A. caccae* from a healthy infant in the Italian cohort and screened multiple carbohydrate sources as potential prebiotics in vitro.[183] We identified several, including amylopectin and inulin, that increased the concentration of butyrate in *A. caccae* cultures with CMA fecal slurries but many of these starches and fibers were poorly soluble and not amenable to use in our gnotobiotic models. Ultimately, we chose the semi-synthetic disaccharide lactulose as the prebiotic to study in vivo. Somewhat to our surprise we found that *A. caccae* engrafted well in mice colonized with a CMA microbiota. Cecal butyrate concentrations were not increased, however, until the *A. caccae* engrafted mice also received prebiotic lactulose, in support of our synbiotic approach. Importantly, we were able to show that treatment of CMA-colonized mice with a synbiotic of *A. caccae* and lactulose reduced the anaphylactic response to sensitization with the cow's milk protein BLG.[183] To evaluate the synbiotic in another microbial and antigenic context, we demonstrated that it also had efficacy in the same therapeutic model of peanut allergy in which we tested the butyrate micelles.[179,183] Exploring the mechanism for the synbiotic's allergy protective effects, we found that treatment with *A. caccae* (with or without lactulose) increased the proportion of RORγt-expressing Foxp3$^+$Tregs in both the ileal- and cecal-colonic mesenteric lymph nodes of CMA-colonized mice. This suggested that *A. caccae* treatment increased Foxp3$^+$RORγt$^+$ Tregs in the mesenteric lymph nodes by a mechanism other than butyrate production, since treatment with *A. caccae* alone did not increase the concentration of cecal butyrate.[183] We discovered that the expression of the epithelial alarmin IL-25 was elevated in sensitized, CMA-colonized, mice and reduced in mice treated with the synbiotic. Tuft cells are the only cellular source of IL-25 in the mouse intestine.[184–186] Recent work has shown that the production of butyrate by commensal bacteria regulates type II immunity by

constraining the differentiation of tuft cells.[187] As mentioned above, butyrate's ability to act as an HDAC inhibitor to epigenetically regulate gene expression has been well documented.[161] Colonization with butyrate-producing bacteria suppressed tuft cell expansion in mice treated with oral succinate. Succinate-induced tuft cell expansion was also reduced in mice with an epithelium-specific deletion of histone deacetylase 3 (HDAC3).[187] Our data therefore suggest that the CMA microbiota primes the epithelium for a pro-allergic response. The brake provided by butyrate's ability to epigenetically regulate the differentiation of tuft cells from crypt stem cells[187] is impaired by the low concentrations of luminal butyrate in CMA-colonized mice, and restored by treatment with the synbiotic, which blocks the progression to type II immunity.

Palforzia™, a low-dose oral immunotherapy (OIT) for peanut[188] is one of only two FDA-approved treatments for food allergies (the other is Xolair™, a monoclonal antibody to IgE administered by repeated subcutaneous injection[189]). Until the approval of Xolair™ this year, OIT has been the standard of care. OIT requires the gradual administration of small, increasing doses of allergen over time. The potential for severe adverse reactions, high drop-out rates, and the failure to induce allergen-specific tolerance (as opposed to transient desensitization) have suggested that OIT alone is not an acceptable long-term therapeutic solution.[190] To improve the efficacy of OIT and mitigate adverse reactions, Moon and colleagues [191] formulated a gel of OVA coupled to the prebiotic fiber inulin. In a murine model of allergic diarrhea, the OVA/inulin gel formulation was a more effective form of prophylactic OIT than OVA alone. Formulation in an inulin gel slowed the transit of OVA in the small intestine and increased its uptake by populations of DC. Mechanistically, OVA/inulin OIT resulted in increased frequencies of $Foxp3^+$ Tregs in the mesenteric lymph nodes and small intestinal lamina propria of the treated mice. Treatment with the OVA/inulin gel restored the ileal contents to a community composition similar to what was seen in naive mice.[191] A butyrogenic role for inulin was not described.

Paradoxically, however, other work showed that an inulin-rich diet can promote allergic responses.[192] In mice, 2 weeks of an inulin-rich diet altered fecal community structure and increased tissue eosinophilia in the gut and airways. Elevated concentrations of bile acids and indoles were detected in the serum of the inulin-diet mice. Inulin altered the production of the bile acid cholic acid, the product of bacterial deconjugation of host-derived taurocholic acid. Elevated bile acid production led, in turn to increased production of IL-33 by stromal cells which stimulated type 2 ILC to produce IL-5 and recruit eosinophils. Cholic acid was sufficient to exacerbate type 2 immunity in a papain-induced model of lung inflammation.[192] Other recent work on bile acids has begun to elucidate their immunoregulatory (and microbiome-modulatory) properties. Primary BAs (PBAs), such as cholic acid, are produced in the liver from the metabolism of cholesterol and stored as taurine or glycine-conjugated bile salts in the gall bladder.[193] PBAs are released into the duodenum after a meal to aid in the digestion of fats; most (95%–97%) are reabsorbed in the ileum. PBA deconjugation is performed by bile salt hydrolases (BSH), which are conserved across the major gut bacterial phyla.[193] The remaining 3%–5% of PBAs continue to the colon where intestinal bacteria convert them into secondary bile acids (SBAs); virtually all of the BA pool in the colon has undergone bacterial modification. The conversion of PBAs to SBAs requires the 7α-dehydroxylation enzymes encoded by the *bai* operon.[194] Interestingly, most of the small number of *bai*-expressing taxa identified to date are in the Clostridia class.[195,196] Strikingly, although *bai*-expressing bacteria are rare, and are at low abundance, they process high concentrations (about 1 mM[197,198]) of colonic PBA, thereby exerting an outsized impact on the overall bacterial metabolite pool. The most abundant SBA end products of this pathway, deoxycholic acid (DCA) and lithocholic acid (LCA), can undergo further modifications; DCA, LCA, and their derivatives comprise 90% of the circulating BA pool in the intestine.[194] Potent immunoregulatory properties have been described for two modified SBA, isoalloLCA, and isoDCA.[199–201] Because they act as detergents, many SBAs can disrupt membrane integrity to selectively lyse, or inhibit the growth of, populations of intestinal bacteria.[193,202] BAs therefore play an important, context-dependent, role in shaping the composition and function of the intestinal microbiota and may be amenable to therapeutic modulation.

The atopic march describes a well-known clinical phenomenon, whereby different site-specific manifestations of allergic disease occur sequentially with age at the population level.[203] Longitudinal studies of patient populations have described a characteristic disease progression, beginning with initial clinical presentation on the skin (atopic dermatitis) and in the gastrointestinal tract (food allergy) in infancy/early childhood and a later appearance in the airways (asthma and allergic rhinitis) at school age.[203,204] Since atopic dermatitis in infancy is often predictive of food allergy later in childhood, interventions, which target the skin microbiome are also of interest. Some evidence suggests that the loss of barrier integrity in the inflamed skin of infants with atopic dermatitis promotes transcutaneous sensitization to food allergens, while early consumption of allergenic foods induces oral tolerance.[205] The skin microbiome is surprisingly diverse; as in the gut, commensal bacterial strains modulate immune homeostasis. In patients with atopic dermatitis pathogenic *Staphylococcus aureus* strains outcompete commensal *Staphylococcus epidermidis* strains to elicit local skin inflammation.[206] *S. aureus* secretes virulence factors which damage keratinocytes and impair skin barrier integrity. Bacteriotherapeutic approaches are being investigated as a topical therapy for atopic dermatitis.[206] As in food allergy, the pathogenesis of atopic dermatitis involves a complex interaction between genetic and environmental factors that are still poorly understood. Successful therapeutic interventions for atopic dermatitis have the potential to halt the march toward food allergy.

## 6 | CONCLUSIONS

The commensal microbiome plays a critical role in regulating immune responses to food, the other major luminal constituent. Modern lifestyle and environmental factors have disrupted homeostatic

host–microbe interactions that co-evolved for millennia. Our knowledge of the microbiome has advanced rapidly, but there is still much to learn. A better understanding of how specific microbial populations protect against, or promote, immune responses to food will inform the development of microbiome-modulating therapeutics with the potential to prevent or treat food allergy.

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## CONFLICT OF INTEREST STATEMENT

C.R.N. is a co-founder and shareholder of ClostraBio, Inc.

## DATA AVAILABILITY STATEMENT

No new datasets were generated or analyzed to prepare this review.

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## REFERENCES

1. Brough HA, Lanser BJ, Sindher SB, et al. Early intervention and prevention of allergic diseases. *Allergy*. 2022;77(2):416-441.
2. US Food and Drug Administration. *Food Allergies: What you Need to Know*. US Food and Drug Administration; 2024.
3. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. *Gastroenterology*. 2015;148(6):1120-1131.e4.
4. Valenta R, Karaulov A, Niederberger V, et al. Molecular aspects of allergens and allergy. *Adv Immunol*. 2018;138:195-256.
5. Warren CM, Sehgal S, Sicherer SH, Gupta RS. Epidemiology and the growing epidemic of food allergy in children and adults across the globe. *Curr Allergy Asthma Rep*. 2024;24(3):95-106.
6. Warren C, Nimmagadda SR, Gupta R, Levin M. The epidemiology of food allergy in adults. *Ann Allergy Asthma Immunol*. 2023;130(3):276-287.
7. Kanchan K, Clay S, Irizar H, Bunyavanich S, Mathias RA. Current insights into the genetics of food allergy. *J Allergy Clin Immunol*. 2021;147(1):15-28.
8. Prioult G, Nagler-Anderson C. Mucosal immunity and allergic responses: lack of regulation and/or lack of microbial stimulation? *Immunol Rev*. 2005;206:204-218.
9. Iweala OI, Nagler CR. The microbiome and food allergy. *Annu Rev Immunol*. 2019;37:377-403.
10. Sonnenburg JL, Sonnenburg ED. Vulnerability of the industrialized microbiota. *Science*. 2019;366(6464):eaaw9255.
11. Sonnenburg ED, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. *Nat Rev Microbiol*. 2019;17(6):383-390.
12. Dominguez-Bello MG, Godoy-Vitorino F, Knight R, Blaser MJ. Role of the microbiome in human development. *Gut*. 2019;68(6):1108-1114.
13. Wilde J, Slack E, Foster KR. Host control of the microbiome: mechanisms, evolution, and disease. *Science*. 2024;385(6706):eadi3338.
14. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. 2016;14(8):e1002533.
15. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*. 2016;164(3):337-340.
16. Pasteur L. Memoirs sur les corpuscles organises qui existent dan's l'atmosphere. Examen de la doctrine des generation spontanees. *Ann Sci Nat*. 1861;16:5-98.
17. Fridericia LS, Freudenthal P, Gudjonnsson S, Johansen G, Schoubye N. Refection, a transmissible change in the intestinal content, enabling rats to grow and thrive without vitamin B in the food. *J Hyg (Lond)*. 1927;27(1):70-102.
18. Bohnhoff M, Drake BL, Miller CP. Effect of streptomycin on susceptibility of intestinal tract to experimental salmonella infection. *Proc Soc Exp Biol Med*. 1954;86(1):132-137.
19. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*. 1958;44(5):854-859.
20. Moore WE, Holdeman LV. Human fecal flora: the normal flora of 20 Japanese-Hawaiians. *Appl Microbiol*. 1974;27(5):961-979.
21. Gingell R, Bridges JW, Williams RT. The role of the gut flora in the metabolism of prontosil and neoprontosil in the rat. *Xenobiotica*. 1971;1(2):143-156.
22. Roediger WE. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut*. 1980;21(9):793-798.
23. Woese CR, Fox GE. Phylogenetic structure of the prokaryotic domain: the primary kingdoms. *Proc Natl Acad Sci USA*. 1977;74(11):5088-5090.
24. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. *Science*. 2005;308(5728):1635-1638.
25. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486(7402):222-227.
26. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486(7402):207-214.
27. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell*. 2005;122(1):107-118.
28. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027-1031.
29. Backhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci USA*. 2007;104(3):979-984.
30. Bauermeister A, Mannochio-Russo H, Costa-Lotufo LV, Jarmusch AK, Dorrestein PC. Mass spectrometry-based metabolomics in microbiome investigations. *Nat Rev Microbiol*. 2022;20(3):143-160.
31. Cheng AG, Ho PY, Aranda-Diaz A, et al. Design, construction, and in vivo augmentation of a complex gut microbiome. *Cell*. 2022;185(19):3617-3636 e3619.
32. Boutard M, Cerisy T, Nogue PY, et al. Functional diversity of carbohydrate-active enzymes enabling a bacterium to ferment plant biomass. *PLoS Genet*. 2014;10(11):e1004773.
33. Lapebie P, Lombard V, Drula E, Terrapon N, Henrissat B. Bacteroidetes use thousands of enzyme combinations to break down glycans. *Nat Commun*. 2019;10(1):2043.

34. El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol*. 2013;11(7):497-504.
35. Donohoe DR, Garge N, Zhang X, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metab*. 2011;13(5):517-526.
36. Royall D, Wolever TM, Jeejeebhoy KN. Clinical significance of colonic fermentation. *Am J Gastroenterol*. 1990;85(10):1307-1312.
37. van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. *Trends Microbiol*. 2021;29(8):700-712.
38. Oliveira RA, Pamer EG. Assembling symbiotic bacterial species into live therapeutic consortia that reconstitute microbiome functions. *Cell Host Microbe*. 2023;31(4):472-484.
39. Reichardt N, Duncan SH, Young P, et al. Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *ISME J*. 2014;8(6):1323-1335.
40. de Goffau MC, Lager S, Sovio U, et al. Human placenta has no microbiome but can contain potential pathogens. *Nature*. 2019;572(7769):329-334.
41. Kennedy KM, Gerlach MJ, Adam T, et al. Fetal meconium does not have a detectable microbiota before birth. *Nat Microbiol*. 2021;6(7):865-873.
42. Kennedy KM, de Goffau MC, Perez-Munoz ME, et al. Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature*. 2023;613(7945):639-649.
43. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010;107(26):11971-11975.
44. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med*. 2016;8(343):343ra382.
45. Shao Y, Forster SC, Tsaliki E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature*. 2019;574(7776):117-121.
46. Reyman M, van Houten MA, van Baarle D, et al. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. *Nat Commun*. 2019;10(1):4997.
47. Ferretti P, Pasolli E, Tett A, et al. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe*. 2018;24(1):133-145.e5.
48. Yassour M, Jason E, Hogstrom LJ, et al. Strain-level analysis of mother-to-child bacterial transmission during the first few months of life. *Cell Host Microbe*. 2018;24(1):146-154.e4.
49. Bogaert D, van Beveren GJ, de Koff EM, et al. Mother-to-infant microbiota transmission and infant microbiota development across multiple body sites. *Cell Host Microbe*. 2023;31(3):447-460.e6.
50. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med*. 2016;22(3):250-253.
51. Korpela K, Helve O, Kolho KL, et al. Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores Normal gut microbial development: a proof-of-concept study. *Cell*. 2020;183(2):324-334.e5.
52. Sela DA, Mills DA. Nursing our microbiota: molecular linkages between Bifidobacteria and milk oligosaccharides. *Trends Microbiol*. 2010;18(7):298-307.
53. Henrick BM, Rodriguez L, Lakshmikanth T, et al. Bifidobacteria-mediated immune system imprinting early in life. *Cell*. 2021;184(15):3884-3898.e11.
54. Selma-Royo M, Dubois L, Manara S, et al. Birthmode and environment-dependent microbiota transmission dynamics are complemented by breastfeeding during the first year. *Cell Host Microbe*. 2024;32(6):996-1010.e4.
55. Moossavi S, Sepehri S, Robertson B, et al. Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. *Cell Host Microbe*. 2019;25(2):324-335.e4.
56. McGuire MK, McGuire MA. Got bacteria? The astounding, yet not-so-surprising, microbiome of human milk. *Curr Opin Biotechnol*. 2017;44:63-68.
57. Backhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*. 2015;17(5):690-703.
58. Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018;562(7728):583-588.
59. Vatanen T, Plichta DR, Somani J, et al. Genomic variation and strain-specific functional adaptation in the human gut microbiome during early life. *Nat Microbiol*. 2019;4(3):470-479.
60. Rao C, Coyte KZ, Bainter W, Geha RS, Martin CR, Rakoff-Nahoum S. Multi-kingdom ecological drivers of microbiota assembly in preterm infants. *Nature*. 2021;591(7851):633-638.
61. Vatanen T, Jabbar KS, Ruohtula T, et al. Mobile genetic elements from the maternal microbiome shape infant gut microbial assembly and metabolism. *Cell*. 2022;185(26):4921-4936.e15.
62. Million M, Raoult D. Linking gut redox to human microbiome. *Hum Microbiome J*. 2018;10:27-32.
63. Beller L, Deboutte W, Falony G, et al. Successional stages in infant gut microbiota maturation. *MBio*. 2021;12(6):e0185721.
64. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med*. 2016;375(5):411-421.
65. Gacesa R, Kurilshikov A, Vich Vila A, et al. Environmental factors shaping the gut microbiome in a Dutch population. *Nature*. 2022;604(7907):732-739.
66. Sessitsch A, Wakelin S, Schloter M, et al. Microbiome interconnectedness throughout environments with major consequences for healthy people and a healthy planet. *Microbiol Mol Biol Rev*. 2023;87(3):e0021222.
67. Gilbert JA, Hartmann EM. The indoors microbiome and human health. *Nat Rev Microbiol*. 2024. doi:10.1038/s41579-024-01077-3. Online ahead of print.
68. Zhou X, Shen X, Johnson JS, et al. Longitudinal profiling of the microbiome at four body sites reveals core stability and individualized dynamics during health and disease. *Cell Host Microbe*. 2024;32(4):506-526.e9.
69. Olm MR, Dahan D, Carter MM, et al. Robust variation in infant gut microbiome assembly across a spectrum of lifestyles. *Science*. 2022;376(6598):1220-1223.
70. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature*. 2016;529(7585):212-215.
71. Vangay P, Johnson AJ, Ward TL, et al. US immigration westernizes the human gut microbiome. *Cell*. 2018;175(4):962-972.e10.
72. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. *Cell*. 2021;184(16):4137-4153.e14.
73. Brosschot TP, Reynolds LA. The impact of a helminth-modified microbiome on host immunity. *Mucosal Immunol*. 2018;11(4):1039-1046.
74. Talbird SE, Carrico J, La EM, et al. Impact of routine childhood immunization in reducing vaccine-preventable diseases in the United States. *Pediatrics*. 2022;150(3):e2021056013.
75. Chung The H, Le SH. Dynamic of the human gut microbiome under infectious diarrhea. *Curr Opin Microbiol*. 2022;66:79-85.
76. Hansen ZA, Vasco K, Rudrik JT, Scribner KT, Zhang L, Manning SD. Recovery of the gut microbiome following enteric infection and persistence of antimicrobial resistance genes in specific microbial hosts. *Sci Rep*. 2023;13(1):15524.

77. Temba GS, Kullaya V, Pecht T, et al. Urban living in healthy Tanzanians is associated with an inflammatory status driven by dietary and metabolic changes. *Nat Immunol*. 2021;22(3):287-300.
78. Morandini F, Perez K, Brot L, et al. Urbanization associates with restricted gut microbiome diversity and delayed maturation in infants. *iScience*. 2023;26(11):108136.
79. Doyle AD, Masuda MY, Pyon GC, et al. Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus. *Allergy*. 2023;78(1):192-201.
80. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. 2015;519(7541):92-96.
81. Panyod S, Wu WK, Chang CT, et al. Common dietary emulsifiers promote metabolic disorders and intestinal microbiota dysbiosis in mice. *Commun Biol*. 2024;7(1):749.
82. Suez J, Cohen Y, Valdes-Mas R, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell*. 2022;185(18):3307-3328.e19.
83. Uzan-Yulzari A, Turta O, Belogolovski A, et al. Neonatal antibiotic exposure impairs child growth during the first six years of life by perturbing intestinal microbial colonization. *Nat Commun*. 2021;12(1):443.
84. Reyman M, van Houten MA, Watson RL, et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. *Nat Commun*. 2022;13(1):893.
85. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol*. 2008;6(11):e280.
86. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. *Trends Immunol*. 2012;33:459-466.
87. Ng KM, Aranda-Diaz A, Tropini C, et al. Recovery of the gut microbiota after antibiotics depends on host diet, community context, and environmental reservoirs. *Cell Host Microbe*. 2019;26(5):650-665.e4.
88. Becattini S, Taur Y, Pamer EG. Antibiotic-induced changes in the intestinal microbiota and disease. *Trends Mol Med*. 2016;22(6):458-478.
89. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131(3):e964-e999.
90. Perdijk O, Butler A, Macowan M, et al. Antibiotic-driven dysbiosis in early life disrupts indole-3-propionic acid production and exacerbates allergic airway inflammation in adulthood. *Immunity*. 2024;57:1939-1954.e7.
91. Patrick DM, Sbihi H, Dai DLY, et al. Decreasing antibiotic use, the gut microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies. *Lancet Respir Med*. 2020;8(11):1094-1105.
92. Cho I, Yamanishi S, Cox L, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*. 2012;488(7413):621-626.
93. Butaye P, Devriese LA, Haesebrouck F. Antimicrobial growth promoters used in animal feed: effects of less well known antibiotics on gram-positive bacteria. *Clin Microbiol Rev*. 2003;16(2):175-188.
94. Van Boeckel TP, Brower C, Gilbert M, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA*. 2015;112(18):5649-5654.
95. Ribado JV, Ley C, Haggerty TD, Tkachenko E, Bhatt AS, Parsonnet J. Household triclosan and triclocarban effects on the infant and maternal microbiome. *EMBO Mol Med*. 2017;9(12):1732-1741.
96. Savage JH, Matsui EC, Wood RA, Keet CA. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. *J Allergy Clin Immunol*. 2012;130:453-460.
97. Nagler-Anderson C, Shi HN. Peripheral nonresponsiveness to orally administered soluble protein antigens. *Crit Rev Immunol*. 2001;21(1–3):121-131.
98. Pabst O, Mowat AM. Oral tolerance to food protein. *Mucosal Immunol*. 2012;5(3):232-239.
99. Gause WC, Urban JFJ, Stadecker MJ. The immune response to parasitic helminths: insights from murine models. *Trends Immunol*. 2003;24:269-277.
100. Shi HN, Ingui CJ, Dodge I, Nagler-Anderson C. A helminth-induced mucosal Th2 response alters nonresponsiveness to oral administration of a soluble antigen. *J Immunol*. 1998;160(5):2449-2455.
101. Shi HN, Liu HY, Nagler-Anderson C. Enteric infection acts as an adjuvant for the response to a model food antigen. *J Immunol*. 2000;165(11):6174-6182.
102. Canesso MC, Castro TBR, Nakandakari-Higa S, et al. Identification of dendritic cell-T cell interactions driving immune responses to food. *bioRxiv*. 2024. 10.1101/2022.10.26.513772
103. Bashir ME, Andersen P, Fuss IJ, Shi HN, Nagler-Anderson C. An enteric helminth infection protects against an allergic response to dietary antigen. *J Immunol*. 2002;169(6):3284-3292.
104. van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet*. 2000;356(9243):1723-1727.
105. Loke P, Harris NL. Networking between helminths, microbes, and mammals. *Cell Host Microbe*. 2023;31(4):464-471.
106. Podolsky DK. Inflammatory bowel disease. *N Engl J Med*. 2002;347(6):417-429.
107. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. *Nat Rev Immunol*. 2003;7:521-533.
108. Bashir ME, Louie S, Shi HN, Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *J Immunol*. 2004;172(11):6978-6987.
109. Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization. *Proc Natl Acad Sci USA*. 2014;111(36):13145-13150.
110. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, et al. A functionally specialized population of mucosal CD103$^+$ DCs induces Foxp3$^+$ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med*. 2007;204(8):1757-1764.
111. Sun CM, Hall JA, Blank RB, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med*. 2007;204(8):1775-1785.
112. Benson MJ, Pino-Lagos K, Rosemblatt M, Noelle RJ. All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J Exp Med*. 2007;204:1765-1774.
113. Hadis U, Wahl B, Schulz O, et al. Intestinal tolerance requires gut homing and expansion of FoxP3$^+$ regulatory T cells in the lamina propria. *Immunity*. 2011;34(2):237-246.
114. Kim KS, Hong SW, Han D, et al. Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science*. 2016;351(6275):858-863.
115. Wesemann DR, Nagler CR. The microbiome, timing, and barrier function in the context of allergic disease. *Immunity*. 2016;44(4):728-738.
116. Parrish A, Boudaud M, Grant ET, et al. *Akkermansia muciniphila* exacerbates food allergy in fibre-deprived mice. *Nat Microbiol*. 2023;8(10):1863-1879.
117. Horowitz A, Chanez-Paredes SD, Haest X, Turner JR. Paracellular permeability and tight junction regulation in gut health and disease. *Nat Rev Gastroenterol Hepatol*. 2023;20(7):417-432.
118. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol*. 2014;14(3):141-153.
119. Worthington JJ, Reimann F, Gribble FM. Enteroendocrine cells-sensory sentinels of the intestinal environment and orchestrators of mucosal immunity. *Mucosal Immunol*. 2018;11(1):3-20.

120. Gerbe F, Jay P. Intestinal tuft cells: epithelial sentinels linking luminal cues to the immune system. *Mucosal Immunol*. 2016;9(6):1353-1359.
121. Johansson ME, Hansson GC. Immunological aspects of intestinal mucus and mucins. *Nat Rev Immunol*. 2016;16(10):639-649.
122. Bevins CL, Salzman NH. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. *Nat Rev Microbiol*. 2011;9(5):356-368.
123. Brodin P. Immune-microbe interactions early in life: a determinant of health and disease long term. *Science*. 2022;376(6596):945-950.
124. Torow N, Hand TW, Hornef MW. Programmed and environmental determinants driving neonatal mucosal immune development. *Immunity*. 2023;56(3):485-499.
125. Al Nabhani Z, Dulauroy S, Marques R, et al. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. *Immunity*. 2019;50(5):1276-1288.e5.
126. Knoop KA, Gustafsson JK, McDonald KG, et al. Microbial antigen encounter during a preweaning interval is critical for tolerance to gut bacteria. *Sci Immunol*. 2017;2(18):eaao1314.
127. Ohnmacht C, Park JH, Cording S, et al. MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORgammat(+) T cells. *Science*. 2015;349(6251):989-993.
128. Akagbosu B, Tayyebi Z, Shibu G, et al. Novel antigen-presenting cell imparts T(reg)-dependent tolerance to gut microbiota. *Nature*. 2022;610(7933):752-760.
129. Parisotto YF, Cabric V, Park T, et al. Thetis cells induce food-specific Treg cell differentiation and oral tolerance. *bioRxiv*. 2024. 10.1101/2024.05.08.592952
130. Kemter AM, Patry RT, Arnold J, et al. Commensal bacteria signal through TLR5 and AhR to improve barrier integrity and prevent allergic responses to food. *Cell Rep*. 2023;42(10):113153.
131. Berni Canani R, Sangwan N, Stefka AT, et al. *Lactobacillus rhamnosus* GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. *ISME J*. 2016;10(3):742-750.
132. Feehley T, Plunkett CH, Bao R, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. *Nat Med*. 2019;25(3):448-453.
133. Cahenzli J, Koller Y, Wyss M, Geuking MB, McCoy KD. Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. *Cell Host Microbe*. 2013;14(5):559-570.
134. Abdel-Gadir A, Stephen-Victor E, Gerber GK, et al. Microbiota therapy acts via a regulatory T cell MyD88/RORgammat pathway to suppress food allergy. *Nat Med*. 2019;25(7):1164-1174.
135. Bao R, Hesser LA, He Z, Zhou X, Nadeau KC, Nagler CR. Fecal microbiome and metabolome differ in healthy and food-allergic twins. *J Clin Invest*. 2021;131(2):e141935.
136. Bunyavanich S, Shen N, Grishin A, et al. Early-life gut microbiome composition and milk allergy resolution. *J Allergy Clin Immunol*. 2016;138(4):1122-1130.
137. Fazlollahi M, Chun Y, Grishin A, et al. Early-life gut microbiome and egg allergy. *Allergy*. 2018;73(7):1515-1524.
138. Savage JH, Lee-Sarwar KA, Sordillo J, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. *Allergy*. 2018;73(1):145-152.
139. Goldberg MR, Mor H, Magid Neriya D, et al. Microbial signature in IgE-mediated food allergies. *Genome Med*. 2020;12(1):92.
140. De Filippis F, Paparo L, Nocerino R, et al. Specific gut microbiome signatures and the associated pro-inflamatory functions are linked to pediatric allergy and acquisition of immune tolerance. *Nat Commun*. 2021;12(1):5958.
141. Campbell E, Hesser LA, Berni Canani R, et al. A lipopolysaccharide-enriched cow's Milk allergy microbiome promotes a TLR4-dependent proinflammatory intestinal immune response. *J Immunol*. 2024;212(4):702-714.
142. Nadjsombati MS, McGinty JW, Lyons-Cohen MR, et al. Detection of succinate by intestinal tuft cells triggers a type 2 innate immune circuit. *Immunity*. 2018;49(1):33-41.e7.
143. Schneider C, O'Leary CE, von Moltke J, et al. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell*. 2018;174(2):271-284.e14.
144. Lei W, Ren W, Ohmoto M, et al. Activation of intestinal tuft cell-expressed Sucnr1 triggers type 2 immunity in the mouse small intestine. *Proc Natl Acad Sci USA*. 2018;115(21):5552-5557.
145. Banerjee A, Herring CA, Chen B, et al. Succinate produced by intestinal microbes promotes specification of tuft cells to suppress Ileal inflammation. *Gastroenterology*. 2020;159(6):2101-2115.e5.
146. Fung C, Fraser LM, Barron GM, et al. Tuft cells mediate commensal remodeling of the small intestinal antimicrobial landscape. *Proc Natl Acad Sci USA*. 2023;120(23):e2216908120.
147. Coutry N, Nguyen J, Soualhi S, et al. Cross talk between Paneth and tuft cells drives dysbiosis and inflammation in the gut mucosa. *Proc Natl Acad Sci USA*. 2023;120(25):e2219431120.
148. Nico KF, Tyner MDW, Howitt MR. Succinate and tuft cells: how does this sensory process interface with food allergy? *J Allergy Clin Immunol*. 2022;150(3):580-582.
149. Watanabe Y, Nagai F, Morotomi M. Characterization of *Phascolarctobacterium succinatutens* sp. nov., an asaccharolytic, succinate-utilizing bacterium isolated from human feces. *Appl Environ Microbiol*. 2012;78(2):511-518.
150. Ogata Y, Suda W, Ikeyama N, Hattori M, Ohkuma M, Sakamoto M. Complete genome sequence of *Phascolarctobacterium faecium* JCM 30894, a succinate-utilizing bacterium isolated from human feces. *Microbiol Resour Announc*. 2019;8(3):e01487-18.
151. Ikeyama N, Murakami T, Toyoda A, et al. Microbial interaction between the succinate-utilizing bacterium *Phascolarctobacterium faecium* and the gut commensal *Bacteroides thetaiotaomicron*. *Microbiology*. 2020;9(10):e1111.
152. Anthamatten L, Rogalla von Bieberstein P, Menzi C, et al. Stratification of human gut microbiomes by succinotype is associated with inflammatory bowel disease status. *bioRxiv*. 2024. 10.1101/2023.11.21.568118
153. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-514.
154. Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. *World Allergy Organ J*. 2015;8(1):4.
155. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407-415.
156. Truong DT, Tett A, Pasolli E, Huttenhower C, Segata N. Microbial strain-level population structure and genetic diversity from metagenomes. *Genome Res*. 2017;27(4):626-638.
157. Sorbara MT, Littmann ER, Fontana E, et al. Functional and genomic variation between human-derived isolates of Lachnospiraceae reveals inter- and intra-species diversity. *Cell Host Microbe*. 2020;28(1):134-146.e4.
158. Henn MR, O'Brien EJ, Diao L, et al. A phase 1b safety study of SER-287, a spore-based microbiome therapeutic, for active mild to moderate ulcerative colitis. *Gastroenterology*. 2021;160(1):115-127 e130.
159. Dsouza M, Menon R, Crossette E, et al. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe*. 2022;30(4):583-598 e588.
160. Rachid R. Evaluating the safety and efficacy of oral encapsulated microbiota transplantation therapy in peanut allergic patients. Study Rec NCT05695261 2024. Accessed February 9, 2024. https://clinicaltrials.gov/study/NCT05695261

161. Kim CH. Control of lymphocyte functions by gut microbiota-derived short-chain fatty acids. *Cell Mol Immunol*. 2021;18(5):1161-1171.
162. Tan JK, Macia L, Mackay CR. Dietary fiber and SCFAs in the regulation of mucosal immunity. *J Allergy Clin Immunol*. 2023;151(2):361-370.
163. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T cell generation. *Nature*. 2013;504(7480):451-455.
164. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci USA*. 2014;111(6):2247-2252.
165. Schulthess J, Pandey S, Capitani M, et al. The short chain fatty acid butyrate imprints an antimicrobial program in macrophages. *Immunity*. 2019;50(2):432-445.e7.
166. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces differentiation of colonic regulatory T cells. *Nature*. 2013;504(7480):446-450.
167. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013;341(6145):569-573.
168. Folkerts J, Redegeld F, Folkerts G, et al. Butyrate inhibits human mast cell activation via epigenetic regulation of FcepsilonRI-mediated signaling. *Allergy*. 2020;75(8):1966-1978.
169. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol*. 2015;8(1):80-93.
170. Kim M, Qie Y, Park J, Kim CH. Gut microbial metabolites fuel host antibody responses. *Cell Host Microbe*. 2016;20(2):202-214.
171. Kim CH. B cell-helping functions of gut microbial metabolites. *Microb Cell*. 2016;3(10):529-531.
172. Tan J, McKenzie C, Vuillermin PJ, et al. Dietary fiber and bacterial SCFA enhance Oral tolerance and protect against food allergy through diverse cellular pathways. *Cell Rep*. 2016;15(12):2809-2824.
173. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity*. 2014;40(6):833-842.
174. Macia L, Mackay CR. Dysfunctional microbiota with reduced capacity to produce butyrate as a basis for allergic diseases. *J Allergy Clin Immunol*. 2019;144(6):1513-1515.
175. Xie L, Alam MJ, Marques FZ, Mackay CR. A major mechanism for immunomodulation: dietary fibres and acid metabolites. *Semin Immunol*. 2023;66:101737.
176. Cait A, Cardenas E, Dimitriu PA, et al. Reduced genetic potential for butyrate fermentation in the gut microbiome of infants who develop allergic sensitization. *J Allergy Clin Immunol*. 2019;144(6):1638-1647.e3.
177. Depner M, Taft DH, Kirjavainen PV, et al. Maturation of the gut microbiome during the first year of life contributes to the protective farm effect on childhood asthma. *Nat Med*. 2020;26(11):1766-1775.
178. Kabil A, Nayyar N, Brassard J, et al. Microbial intestinal dysbiosis drives long-term allergic susceptibility by sculpting an ILC2-B1 cell-innate IgE axis. *J Allergy Clin Immunol*. 2024. doi:10.1016/j.jaci.2024.07.023. Online ahead of print.
179. Wang R, Cao S, Bashir MEH, et al. Treatment of peanut allergy and colitis in mice via the intestinal release of butyrate from polymeric micelles. *Nat Biomed Eng*. 2023;7(1):38-55.
180. Byndloss MX, Olsan EE, Rivera-Chavez F, et al. Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science*. 2017;357(6351):570-575.
181. Moens F, Verce M, De Vuyst L. Lactate- and acetate-based cross-feeding interactions between selected strains of Lactobacilli, Bifidobacteria and colon bacteria in the presence of inulin-type fructans. *Int J Food Microbiol*. 2017;241:225-236.
182. Chia LW, Mank M, Blijenberg B, et al. Cross-feeding between *Bifidobacterium infantis* and *Anaerostipes caccae* on lactose and human milk oligosaccharides. *Benef Microbes*. 2021;12(1):69-83.
183. Hesser LA, Puente AA, Arnold J, et al. A synbiotic of *Anaerostipes caccae* and lactulose prevents and treats food allergy in mice. *Cell Host Microbe*. 2024;32:1163-1176.e6.
184. Gerbe F, Sidot E, Smyth DJ, et al. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature*. 2016;529(7585):226-230.
185. Howitt MR, Lavoie S, Michaud M, et al. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science*. 2016;351(6279):1329-1333.
186. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature*. 2016;529(7585):221-225.
187. Eshleman EM, Rice T, Potter C, et al. Microbiota-derived butyrate restricts tuft cell differentiation via histone deacetylase 3 to modulate intestinal type 2 immunity. *Immunity*. 2024;57(2):319-332 e316.
188. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018;379(21):1991-2001.
189. Wood RA, Togias A, Sicherer SH, et al. Omalizumab for the treatment of multiple food allergies. *N Engl J Med*. 2024;390(10):889-899.
190. Dantzer JA, Mudd K, Wood RA. Long-term outcomes of peanut immunotherapy in children. *J Allergy Clin Immunol Pract*. 2020;8(5):1753-1756 e1752.
191. Han K, Xie F, Animasahun O, et al. Inulin-gel-based oral immunotherapy remodels the small intestinal microbiome and suppresses food allergy. *Nat Mater*. 2024. doi:10.1038/s41563-024-01909-w. Online ahead of print.
192. Arifuzzaman M, Won TH, Li TT, et al. Inulin fibre promotes microbiota-derived bile acids and type 2 inflammation. *Nature*. 2022;611(7936):578-584.
193. Collins SL, Stine JG, Bisanz JE, Okafor CD, Patterson AD. Bile acids and the gut microbiota: metabolic interactions and impacts on disease. *Nat Rev Microbiol*. 2023;21(4):236-247.
194. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*. 2006;47(2):241-259.
195. Vital M, Rud T, Rath S, Pieper DH, Schluter D. Diversity of bacteria exhibiting bile acid-inducible 7alpha-dehydroxylation genes in the human gut. *Comput Struct Biotechnol J*. 2019;17:1016-1019.
196. Cai J, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. *Cell Host Microbe*. 2022;30(3):289-300.
197. Funabashi M, Grove TL, Wang M, et al. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. *Nature*. 2020;582(7813):566-570.
198. Hamilton JP, Xie G, Raufman JP, et al. Human cecal bile acids: concentration and spectrum. *Am J Physiol Gastrointest Liver Physiol*. 2007;293(1):G256-G263.
199. Campbell C, McKenney PT, Konstantinovsky D, et al. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. *Nature*. 2020;581(7809):475-479.
200. Hang S, Paik D, Yao L, et al. Bile acid metabolites control TH17 and Treg cell differentiation. *Nature*. 2019;576(7785):143-148.
201. Li W, Hang S, Fang Y, et al. A bacterial bile acid metabolite modulates T(reg) activity through the nuclear hormone receptor NR4A1. *Cell Host Microbe*. 2021;29(9):1366-1377 e1369.
202. Devlin AS, Fischbach MA. A biosynthetic pathway for a prominent class of microbiota-derived bile acids. *Nat Chem Biol*. 2015;11(9):685-690.
203. Davidson WF, Leung DYM, Beck LA, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "atopic dermatitis and the atopic march: mechanisms and interventions". *J Allergy Clin Immunol*. 2019;143(3):894-913.

204. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112(6 Suppl):S118-S127.
205. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of P, Children Study T. Factors associated with the development of peanut allergy in childhood. *N Engl J Med*. 2003;348(11):977-985.
206. Tham EH, Chia M, Riggioni C, Nagarajan N, Common JEA, Kong HH. The skin microbiome in pediatric atopic dermatitis and food allergy. *Allergy*. 2024;79(6):1470-1484.

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