Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2019 January ; 16(1): 7–18. doi:10.1038/s41575-018-0064-z.

Mechanisms by which gut microorganisms influence food sensitivities

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Abstract

Finely tuned mechanisms enable the gastrointestinal tract to break down dietary components into nutrients without mounting, in the majority of cases, a dysregulated immune or functional host response. However, adverse reactions to food have been steadily increasing, and evidence suggests that this process is environmental. Adverse food reactions can be divided according to their underlying pathophysiology into food intolerances, when, for instance, there is deficiency of a host enzyme required to digest the food component, and food sensitivities, when immune mechanisms are involved. In this Review, we discuss the clinical and experimental evidence for enteric infections and/or alterations in the gut microbiota in inciting food sensitivity. We focus on mechanisms by which microorganisms might provide direct pro-inflammatory signals to the host promoting breakdown of oral tolerance to food antigens or indirect pathways that involve the metabolism of protein antigens and other dietary components by gut microorganisms. Better understanding of these mechanisms will help in the development of preventive and therapeutic strategies for food sensitivities.

Adverse reactions to food, expressed as food sensitivity or food intolerance, are on the rise^{1–3}. This increase in prevalence cannot be explained by genetic drift, suggesting a critical role of yet unknown environmental factors as modifiers of disease expression⁴. Studies have linked food sensitivities to a variety of microbial signals that could be induced by enteric infections or alterations in the commensal gut microbiota^{4,5}. However, the specific mechanisms behind these associations remain unclear. In this Review, we examine two

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Author contributions

All authors contributed to all aspects of this manuscript.

Competing interests

The authors declare no competing interests.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Reviewer information

Nature Reviews Gastroenterology & Hepatology thanks M. D. Kulis, H. Sampson and H. Tlaskalova-Hogenova for their contribution to the peer review of this work.

major pathways of food sensitivities, diet–microorganism and host–microorganism interactions, and discuss the mechanistic evidence through which they can favour specific adverse reactions to food. Protein antigens in particular can become substrates of gut microorganism metabolism, which can result in altered antigenicity⁶ or in the production of metabolites that directly affect tolerogenic responses⁷. We also discuss treatment strategies designed to target these pathways that could be developed to prevent or better treat food sensitivities⁸.

Adverse reactions to food

It is estimated that one-fifth of the population world-wide experiences adverse reactions to dietary components¹. Manifestations are diverse depending on the underlying aetiology and pathophysiological processes involved¹ (FIG. 1). Food intolerances involve non-immune mechanisms, such as lactose maldigestion, in which there is an inability to break down the disaccharide lactose owing to primary or secondary deficiency of β -galactosidase (lactase). As a consequence, undigested lactose reaches the colon, where it is fermented by the gut microbiota, leading to gas production (hydrogen, carbon dioxide and methane) and bloating⁹. In other clinical entities, such as functional gastrointestinal disorders for which food is often suspected to be a trigger, the specific food components and underlying mechanisms responsible for symptom generation remain unclear^{10–12}. Some of these patients do not receive a conclusive diagnosis even following placebo-controlled food challenge. It remains uncertain whether this difficulty in reaching a conclusive diagnosis results from insufficient laboratory diagnostics or whether such patients have central nervous system-driven mechanisms (nocebo effect) that are not identifiable by diagnostic methods currently available¹³.

Food sensitivities with allergic pathophysiology involve immunoglobulin E (IgE) mechanisms, non-IgE-mediated mechanisms or a combination of both (FIG. 1). IgE-mediated food allergy requires sensitization characterized by production of food allergen-specific IgE¹⁴. Upon re-exposure to the allergen, allergen-specific IgE, which is bound to Fc ϵ RI (also known as FCER1A) on mast cells and basophils, becomes crosslinked and releases mediators, such as histamine, that cause acute symptoms¹⁴. A strong response to the allergen could lead to anaphylaxis, which is defined as a severe allergic reaction of rapid onset affecting multiple tissues that can cause death¹⁴. Non-IgE-mediated food allergy includes different medical conditions such as protein-induced enterocolitis syndrome and food protein-induced proctocolitis. Although they are classified as non-IgE-mediated diseases, some studies suggest that there is mucosal IgE production but at insufficient circulating levels to be detected¹⁵. In contrast to well-defined IgE-mediated food allergy, the diagnostic approaches and immune mechanisms underlying these conditions are not well understood, although TNF has been implicated according to evidence^{15–17}. Another group of chronic conditions with allergic pathophysiology and poorly understood mechanisms involving both IgE and non-IgE responses includes cow's milk protein allergy, eosinophilic oesophagitis and gastroenteritis. In eosinophilic oesophagitis and gastroenteritis, the nature of the food allergen remains undetermined^{1,14}. On the other hand, coeliac disease is a well-characterized CD4⁺ T cell-mediated food sensitivity with autoimmune-like features triggered by ingestion of gluten-containing cereals in genetically predisposed individuals

harbouring *HLA-DQ2* and *HLA-DQ8* genes¹⁸. In addition to coeliac disease, non-allergy, non-coeliac wheat sensitivity (NCWS) has become a common condition¹⁹. The prevalence of NCWS has been reported to vary from 0.6–6.0% in Western populations and up to 13% if self-reported NCWS is considered^{20–23}. However, the prevalence of NCWS cannot be estimated with confidence owing to the lack of biomarkers and specific diagnostics²⁴. Gluten, and other components in wheat, including fructans and α -amylase-trypsin inhibitors (ATIs), have been identified as potential culprits for the induction of symptoms^{25–27}. For instance, ATIs engage the Toll-like receptor 4 (TLR4)–protein MD2 (also known as LY96)–CD14 complex, lead to upregulation of maturation markers and elicit release of pro-inflammatory cytokines that lead to inflammation^{27,28}.

As with other food sensitivities and autoimmune diseases^{29–31}, the prevalence of coeliac disease is increasing worldwide^{2,32}. Because not all people with genetic risk develop coeliac disease, and because the increase in prevalence has been too quick to be explained by genetic drift, environmental factors, such as introduction of gluten to infant diets (timing, amount and frequency), breastfeeding patterns, alterations in the gut microbiota (dysbiosis) and infections, have been suspected^{4,33–35}.

Microbial environmental factors

Several groups have reported the association of food sensitivity with practices that can affect intestinal microbiota composition such as early food behaviours, antibiotic intake or caesarean delivery^{36–38}. In coeliac disease, results from prospective birth cohort studies have been published; however, the studies do not support a statistically significant effect of early feeding practices on coeliac disease development^{39,40}. Although the conclusions do not apply to the general population, follow-up analyses are beginning to raise the hypothesis that a combination of factors might have a role. Indeed, genetic and epidemiological studies showed an association between viral and bacterial infections and the onset of coeliac disease and food allergies^{41–46}, suggesting that repeated microbial infections early in life trigger food sensitivities, particularly in individuals with more moderate genetic predisposition^{34,47,48}. A prospective study provided evidence that an increased frequency of rotavirus infections, which generally affects the small intestine and leads to a transient increased intestinal permeability, predicts increased risk of coeliac disease autoimmunity in genetically predisposed individuals carrying HLA risk alleles for coeliac disease and type 1 diabetes mellitus (T1DM)⁴¹. Interestingly, intestinal rotavirus infection is also implicated in the autoimmunity leading to T1DM⁴⁹. It remains to be determined whether rotavirus vaccination can prevent the onset of coeliac disease, as inconsistent findings have been reported^{50,51}. Consistent with the hypothesis that infection might have a role in coeliac disease aetiology, studies identified the occurrence of small intestinal *Campylobacter jejuni* or adenoviral infection, as well as influenza diagnosis or hepatobiliary virus infections such as hepatitis C, to be substantive risk factors in the development of coeliac disease^{43,45,52,53}. Shi et al.⁴⁸ have also shown that enteric infections by helminths can act as an adjuvant for the response to dietary antigens, which has implications for allergic responses to food. It will be important to investigate the effect of microbial infections early in life, as even a transitory gastro-intestinal infection in the vulnerable neonatal or infant period is potentially able to disturb the local mucosal and systemic immature immune system.

In addition to the support provided by clinical and epidemiological studies for an association between intestinal bacterial and viral infections and food sensitivities^{54–62} (TABLE 1), the role of a dysbiotic gut microbiota has also been evoked. Indeed, several groups have reported intestinal dysbiosis in coeliac disease and food allergy^{56–59,62–65}. For instance, it has been shown that changes in key bacterial groups in infancy were associated with the development of food allergy later in life. One study suggested that a specific intestinal microbial signature with a positive correlation between the genus *Clostridium* sensu stricto and serum-specific IgE was able to distinguish between infants with IgE-mediated food allergy and those without IgE mediation⁶⁶. In addition, coeliac disease-associated dysbiosis seems to be characterized by Proteobacteria expansion and the presence of opportunistic pathogens in the proximal small intestine⁶⁷. Animal studies have provided some mechanistic insight and support the notion that responses to different antigens or allergens can be modulated by the microbial milieu of the intestine^{68–73}. The bulk of mechanistic evidence arises from basic studies that elucidate interactions of specific microorganisms with the antigen or allergen itself, as well as the imprinting of pro-inflammatory or tolerance induction in the host by microorganisms. The following sections expand on these concepts.

Microorganism-diet interactions

A study in humans demonstrated that long-term dietary patterns constitute an important determinant of gut microbiota enterotypes⁷⁴. Others indicated that short-term diet alters microbial community structure⁷⁵, gene expression⁷⁵ and metabolite production^{76,77}. Studies in animal models have linked the intake of omega-3 fatty acids, and of prebiotic (galactooligosaccharides or inulin) exposure during perinatal and post-weaning periods, with the induction of beneficial changes in gut microbiota-derived metabolites associated with tolerance mechanisms that decrease allergic sensitization^{78,79}. However, the exact compositional characteristics of a beneficial gut microbiota, as well as the mechanisms by which those changes prevent disease, have not been completely elucidated. Dietary food components that are neither absorbed nor metabolized by the host become bacterial substrates, which subsequently leads to the production of bacterial metabolites, such as the short-chain fatty acid (SCFA) butyrate⁸⁰ (FIG. 2). In addition, the gut microbiota has the capacity to modify the chemical structures of numerous dietary molecules, including allergens or antigens⁶.

Immunogenicity of food antigens.

The intestinal microbiota is considered a metabolic organ that vastly complements the host's metabolic activities⁸¹. One mechanism through which bacteria could affect immune responses to dietary components is through bacterial metabolism of antigens. This aspect is of particular relevance in coeliac disease, in which proteolytic-resistant gluten proteins are the undeniable trigger of T cell-mediated inflammation⁸². Gluten is a mix of proteins rich in proline and glutamine residues that confer unusual resistance to degradation by mammalian enzymes⁸². This incomplete digestion generates, in vitro, high-molecular-mass oligopeptides, which, when bound to antigen-presenting cells (APCs), are capable of activating a T cell response associated with coeliac disease⁸³. These large peptides constitute attractive substrates for energy by bacteria colonizing the gastrointestinal tract. Several

studies have shown that the human gastrointestinal tract, including the proximal small intestine, harbours gluten-degrading bacteria such as *Rothia* spp. or *Lactobacillus* spp. that are able to utilize non-digested gluten peptides^{84–88}. Caminero et al.⁶ have demonstrated that, in addition to mammalian enzymes, duodenal bacteria participate in gluten metabolism in vivo. Indeed, depending on the type of bacteria present, the end result will be increased or reduced immunogenicity of the produced peptides⁶ (FIG. 2). For instance, specific opportunistic pathogens such as *Pseudomonas aeruginosa* further degrade digestive protease-modified gluten peptides, producing shorter peptides that retain immunogenic sequences. These bacterially modified peptides translocate through the intestinal epithelial barrier better than peptides produced by human digestive proteases, a mechanism that might facilitate the interaction of peptides with the immune system of the host. By contrast, core members of the human duodenal microbiota such as *Lactobacillus* spp. can degrade and detoxify gluten peptides produced by human or opportunistic pathogen proteases⁶. Thus, there exist complex and sequential metabolic events in which mammalian and bacterial proteases synergize with each other to produce a diverse peptide output with variable immunogenic capacity. Interestingly, *Lactobacillus* spp., which predominately reside in the small intestine⁸⁹, have been reported to be more abundant and diverse in healthy individuals than in patients with coeliac disease⁵⁷. Further studies are required to test whether this reduced abundance of lacto-bacilli in patients with coeliac disease is either caused by an ongoing (gluten-induced) inflammation and restored upon a gluten-free diet or whether restoring the presence of lactobacilli improves the gluten-induced pathophysiology. Interestingly, viral or bacterial intestinal infection in mice could suppress the abundance of certain microbial groups involved in gluten metabolism such as *Lactobacillus* spp., thereby affecting coeliac disease onset⁹⁰.

Modification of gluten by the intestinal microbiota is not limited to its degradation. Gluten deamidation — a chemical reaction that removes an amide functional group in the amino acids asparagine or glutamine — by human transglutaminase 2 (TGase2; also known as TGM2), the coeliac disease-associated autoantigen, is a key step in the disease process⁹¹. TGase2 converts glutamine residues to glutamate, which increases peptide binding affinity to HLA-DQ2 or HLA-DQ8 heterodimers expressed on APCs that initiate the CD4⁺ T cell-mediated inflammation characteristic of coeliac disease. In a study published in 2017, it was shown that transamidation of gluten by microbial transglutaminase from *Streptomyces mobaraensis* could reduce the immunogenicity of gluten⁹². Thus, the notion is beginning to emerge that microbial composition is a key factor in modulating the immunogenicity of dietary antigens. This aspect could apply to other food sensitivities, as many food allergens, such as egg and peanut proteins, are resistant to degradation by mammalian proteases⁹³. However, further studies are required to determine whether all allergens or antigens within a specific food (for example, the greater than ten allergens in peanut protein or the multiple immunogenic peptides described in coeliac disease)⁹⁴ could be fully degraded or metabolized by microbial ecosystems to a degree that effectively improves clinical symptoms. Thus, although questions based on colonization capacity and stability of the strains in the human gastrointestinal tract can be raised, microorganisms with the ability to degrade or modify immunogenic food antigens or allergens could be an attractive field for therapeutic development in the future.

Metabolites with immunomodulatory function.

Under steady state, the intestinal microbiota has an essential role in maintaining a tolerogenic gut environment that prevents an inflammatory response against foreign antigens, mainly by promoting epithelial integrity and tolerogenic regulatory T (T_{reg}) cell function⁹⁵. Many of these effects are mediated by immunomodulatory metabolites that result from the bacterial metabolism of dietary substrates (FIG. 2). Bacterial metabolic products such as SCFAs or tryptophan-derived metabolites have been shown to directly regulate mucosal immune function and the intestinal barrier, affecting the predisposition to food sensitivity^{96,97}. Specifically, alterations of these metabolites have been described in patients with food sensitivities^{57,98}.

Butyrate, which is derived from the bacterial metabolism of dietary fibre⁹⁹, regulates both the proportions and the functional capabilities of forkhead box protein P3 (FOXP3)⁺ T_{reg} cells^{7,100,101}, which are central to the maintenance of tolerance to food antigens or allergens^{102,103}. A study in mice showed that high-fibre feeding reshaped gut microbial ecology and increased the release of SCFAs, improving oral tolerance to food allergens by activating retinal dehydrogenase activity in CD103⁺ dendritic cells (DCs)¹⁰⁴. This feeding regimen also boosted IgA production and enhanced T follicular helper and mucosal germinal centre responses, regulating numerous protective pathways in the gastrointestinal tract that are necessary for immune non-responsiveness to food antigens¹⁰⁴. The importance of bacterial metabolites in maintaining epithelial barrier integrity under tissue distress was demonstrated in a study by Fukuda et al.¹⁰⁵ who showed that the SCFA acetate was able to promote epithelial integrity during enteropathogenic infection in mice. In agreement with this finding, others showed that members of the Firmicutes phylum (such as Clostridia), through IL-22 induced by bacteria, protected against allergic sensitization to food allergens by regulating innate lymphoid cell function and intestinal epithelial permeability⁷². In addition, IL-15, a pro-inflammatory cytokine upregulated in the epithelium and the lamina propria in coeliac disease¹⁰⁶, led to dysbiosis with an overall reduction of butyrate and a decreased abundance of butyrate-producing bacteria, which was associated with a higher susceptibility to intestinal inflammation¹⁰⁷. Findings also indicate that butyrate quenches the inhibitory effects of IL-12 on FOXP3⁺ T_{reg} cell expansion (B.J., unpublished observations), which was shown to be upregulated by mucosal DCs in the presence of high IL-15 together with retinoic acid (RA) and shown to lead to loss of tolerance (LOT) to gluten¹⁰⁶. In food allergy, dietary intervention with a butyrate-producing *Lactobacillus* strain for 6 months alleviated cow's milk allergy symptoms in infants and was associated with changes in the composition of the intestinal micro-biota¹⁰⁸. Furthermore, it was shown that *Bifidobacterium* spp., via production of acetate, promoted intestinal epithelial integrity and protected against lethal infection, potentially alleviating food allergy in mice by inducing apoptosis in mast cells¹⁰⁵.

Another emerging example relates to the production of aryl hydrocarbon receptor (AhR) ligands by microbial metabolism of dietary substrates rich in tryptophan¹⁰⁹. The indole group in the amino acid tryptophan is metabolized by bacteria, such as *Lactobacillus* spp. or *Streptococcus* spp., releasing potent stimulators (3-indolepropionic acid, indole-3-carboxaldehyde or indole) of AhR^{65,97}. This receptor is a cytosolic ligand-dependent

transcription factor that is highly expressed in the intestinal epithelium and other immune cells that regulate important homeostatic functions in the gut, including maintenance of barrier function and maturation of the immune system^{109,110}. Activation of AhR positively affects DC phenotype and function during allergic sensitization and could lead to protection in a mouse peanut allergy model^{111–113}. Although using dietary interventions and their effects on the gut microbiota to avoid food sensitivities is still far from clinical application, deciphering beneficial bacterial molecules and their dietary precursors is of high interest, as it could lead to sensible dietary guidelines in the future.

Other microbial determinants.

Commensal intestinal bacteria protect the host from developing adverse food reactions. Specifically, direct modulation of peripherally derived FOXP3⁺ T_{reg} (pT_{reg}) cell responses by commensals has been described. For instance, *Bacteroides fragilis* was shown to promote IL-10 production¹¹⁴ and pT_{reg} cell differentiation^{115,116}. Accordingly, germ-free mice have been shown to develop more severe allergies¹¹⁷ and more severe immunopathology in mouse models of gluten sensitivity⁶⁸. Live bacteria, but also dead bacteria or bacterial components such as lipopolysaccharides present in the diet of germ-free mice, can promote T_{reg} cells^{118,119}. The use of certain live bacteria as a probiotic treatment with either mouse-derived or human-derived strains attenuated food sensitivity^{71,72,120,121}. For instance, prenatal and postnatal supplementation of *Bifidobacterium* spp., such as *Bifidobacterium breve* M-16V and *Bifidobacterium longum* BB536, has been suggested to prevent allergic diseases¹²², which is in line with evidence that signals from the commensal microbiota suppress IgE production and basophil development¹²³. However, the mechanisms behind these findings are not always well described. Combinations of probiotic bacteria such as VSL#3 (*Lactobacillus plantarum*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *B. breve*, *B. longum*, *B. longum* subsp. *infantis* and *Streptococcus thermophilus*) have been tested in both food allergy and coeliac disease on the basis of their immunomodulatory capacity and their ability to degrade wheat protein^{124–126}. However, currently, these products cannot be recommended in clinical practice, as it is unknown whether such probiotic preparations are able to degrade the specific immunogenic regions of gluten. Moreover, their clinical efficacy has not been rigorously tested. Production of immunomodulatory molecules such as SCFAs by probiotic strains could confer protection to food components¹⁰⁵. However, other bacterial compounds produced dependently or independently from dietary substrate metabolism could be of interest. Production of specific anti-inflammatory molecules such as immunomodulatory serpins produced by *B. longum* NCC2705 has been shown to prevent gluten-induced immunopathology in mice¹²⁷. Interestingly, serpin expression has been identified to be specifically reduced in the small intestine of patients with coeliac disease¹²⁸. Furthermore, extracellular vesicle-derived protein from *B. longum* KACC91563 was shown to alleviate food allergy through mast cell suppression¹²⁹. On other hand, probiotics have been proposed in combination with oral immunotherapy for food allergy. For instance, oral immunotherapy with peanut proteins and *Lactobacillus* strains induced long-lasting tolerance in children with peanut allergy in a randomized pilot study of 62 children stratified by age¹³⁰. The use of dead bacteria such as *Escherichia coli* for encapsulation of modified peanut protein has also been proposed¹³¹.

Induction of pro-inflammatory events

The default immune response to ingested dietary antigens is both local and systemic active unresponsiveness, an essential physiological process in the small intestine referred to as oral tolerance, which protects mammals from developing food sensitivities^{132,133}. Environmental factors, such as enteric pathobionts, have the capacity to dictate the type of mucosal immune response and can shift the tolerogenic regulatory immune response towards dietary antigens into an inflammatory T helper cell response, which consequently results in LOT to that antigen. Thus, the question arises as to how microbial infections can affect molecular host signalling pathways that are involved in the development of LOT to dietary antigens such as gluten in coeliac disease or in the development of other food sensitivities or allergies.

Barrier dysfunction and innate immunity.

Intestinal epithelial cells (IECs) have an important role in mediating oral tolerance to dietary antigens or allergens by producing cytokines and/or signalling mediators that affect the cell types involved in oral tolerance, as well as in maintaining an intact epithelial barrier, which restricts access of larger, potentially immunogenic, macromolecules^{134–136}. In addition, coeliac disease is characterized by a leaky intestinal barrier^{137,138}, and an increased intestinal permeability is suspected to trigger the sensitization towards dietary antigens in food allergy¹³⁹. Most importantly, it is suspected that frequent microbial infections involving the intestinal tract could increase intestinal permeability¹³⁴. Many pathogens interact with the intestinal barrier, underlining the importance of bacterial–host interactions in both health and disease. These effects might result from direct modification of tight junction proteins, activation of receptors in epithelial cells such as Toll-like receptors (TLRs) or different kinase-mediated effects^{140–143}. Pathogens might alter the intestinal mucous layer by either improving mucus degradation or inhibiting the normal commensal cues for mucus production¹⁴⁴. Moreover, the intestinal epithelium influences tolerance to microbial or food antigens and/or allergens by conditioning mucosal APCs towards either development of CD103⁺ tolero-genic DCs, by releasing transforming growth factor- β (TGF β) and RA^{145,146} under homeostatic conditions, or a pro-inflammatory T helper 1 (T_H1) cell or T_H2 cell response when barrier function is disrupted¹⁴⁷.

Loss of epithelial barrier function and innate immunity is fundamental to the pathogenesis of food sensitivities. IECs and innate immune cells of the lamina propria express pattern recognition receptors (PRRs) that endow them with the ability to recognize microbial products or pathogen-associated molecular patterns (PAMPs). The role of PRRs in food sensitivity is complex. Detection of PAMPs enables the intestinal epithelium to activate signalling pathways that could lead to food sensitivities¹⁴⁸. Furthermore, it has been suggested that dietary antigens can also be recognized by PRRs¹⁴⁹. In this context, the previously mentioned wheat proteins, ATIs, could have an important role, particularly for coeliac disease and NCWS^{27,28}. On the other hand, TLRs, such as TLR4, are thought to be essential for the maintenance of intestinal homeostasis¹⁵⁰. For instance, TLR4-dependent signals provided by the microbiota inhibit the development of allergic responses to food allergens according to experimental evidence³⁸. There is also an association of food sensitivities with single nucleotide polymorphisms in microbial sensing receptors such as

TLR6 or TLR9 (REFS^{151–153}). Thus, depending on the context, PRRs could have a protective or pathogenic role in the response to food antigens.

Studies have linked the role of innate lymphoid cells (ILCs) to food sensitivities^{154–158}. ILCs are uniquely capable of responding to the gut microbiota owing to their tissue localization and rapid primary responses¹⁵⁹. It has been described that commensal microorganisms promote a crosstalk between innate myeloid and lymphoid cells that leads to immune homeostasis in the intestine¹⁶⁰. However, the implications of this crosstalk in food sensitivities have not been addressed. Chua et al. have shown that intestinal dysbiosis featuring abundance of *Ruminococcus gnavus* is associated with allergic diseases in infants through activation of group 2 ILCs (ILC2s)¹⁶¹. IL-25-producing intestinal epithelial tuft cells have been shown to initiate intestinal ILC2 responses to parasitic worm infection in animal models¹⁶². However, it is too early to make firm conclusions about the role of ILCs in food sensitivities.

T helper 1 cell-mediated immunity to food antigens.

In the absence of tissue distress, mucosal CD103⁺ DCs, which are at high frequency in the small intestinal lamina propria and mesenteric lymph nodes, present luminal dietary antigen to naive CD4⁺ T helper cells and promote their differentiation into pT_{reg} cells via a TGFβ-dependent and RA-dependent mechanism^{163,164}. Esterházy et al.¹⁴⁶ demonstrated that the mucosal interferon regulatory factor 8 (IRF8)-dependent CD103⁺CD11b[−] DC subset contains the most potent inducers of pT_{reg} cells and oral tolerance under steady state conditions and that this subset displays the most potent tolerogenic gene expression pattern, including high expression of genes encoding TGFβ and the RA-catalysing enzyme retinal dehydrogenase 2 (RALDH2). The maturation and maintenance of this highly tolerogenic CD103⁺ DC subset are dependent on enteric environmental conditions¹³², and an alteration of RALDH2 activity is associated with impaired oral tolerance in animal models¹⁶⁵. However, it is intriguing that the DC subset with the greatest tolerogenic potential also expresses pro-inflammatory IL-12 and IL-15 and drives T_H1 cell responses to intestinal infections^{166,167}. This DC subset also expresses *Thr9*, which binds bacterial and viral DNA, and triggers signalling cascades that lead to a pro-inflammatory cytokine response¹⁴⁶ (FIG. 3).

Intestinal inflammation abrogates the ability of CD103⁺ DCs to promote pT_{reg} cell differentiation¹⁶⁸, and under tissue distress, such as dermal parasitic *Leishmania major* infection, the CD103⁺CD11b[−] DC subset was shown to produce IL-12 and to drive T_H1 cell immunity in mice¹⁶⁶. Similarly, fungal infection with *Encephalitozoon cuniculi* induced a pro-inflammatory programme in lamina propria-residing, IL-12-producing CD103⁺CD11b[−]CD8⁺ DCs in mice¹⁶⁹. This finding is in accordance with a study showing that enteric type 1 strain Lang (T1L) reovirus infection⁵ induced pro-inflammatory IL-12 production by mucosal CD103⁺CD11b[−] DCs, which drove T_H1 cell responses to the dietary antigen gluten in an IRF1-dependent manner in animal models. Interestingly, this study also suggests that whereas IRF1 is required to induce T_H1 cell responses to dietary antigens, it is not required for blocking the pT_{reg} cell induction that requires type I interferon.

Reovirus-mediated inflammatory T helper 1 cell response to dietary antigens.

Some of the hypotheses of an infectious aetiology of coeliac disease include a reovirus-triggered induction of pro-inflammatory type I interferon^{83,170} or virus-mediated upregulation and release of the enzyme tissue transglutaminase¹⁷¹. In a 2017 study⁵, these associations were moved towards causality, and as a consequence of virus–host interactions, the pT_{reg} cell response was abrogated, and a pathogenic T_H1 cell response to gluten was induced instead. Importantly, two reovirus strains belonging to the same family of Reoviridae had different capacities to induce LOT, suggesting that particular viral genes interacting with the host can induce signalling pathways that lead to LOT. Intriguingly, other findings (B.J., unpublished observations) suggest that certain viruses, other than reovirus, can also induce LOT through manipulation of tolerogenic DCs presenting dietary antigens. These findings suggest that studying the viral genes that correlate with LOT by generating viral reassortants or mutants will help to understand the underlying mechanisms and to target specific pathways. Mechanistically, T1L reovirus induced LOT by blocking pT_{reg} cell induction through type I interferon-mediated pathways. By contrast, T_H1 cell induction in response to oral antigen was independent of type I interferon but required the transcription factor IRF1 in the CD103⁺CD11b[−] DCs that present oral antigen and produce IL-12 upon T1L reovirus infection. Furthermore, patients with coeliac disease had substantially higher anti-reovirus antibody titres than patients without coeliac disease, and intestinal mucosal *IRF1* expression levels of patients with coeliac disease were associated with anti-reovirus antibody titres⁵, suggesting that antecedent virus–host interactions can initiate long-lasting changes in immune homeostasis associated with high mucosal *IRF1* expression.

Future studies need to elucidate whether other enteropathogens, besides T1L reovirus, can induce a pro-inflammatory programme in CD103⁺CD11b[−] DCs, thereby suppressing a tolerogenic pT_{reg} cell response and instead driving a T_H1 cell response that leads to LOT to food antigens⁵ and whether this process could have important implications in other food sensitivities¹⁷².

The role of IL-15 in T helper 1 cell induction.

Another pathway that can be induced by microbial triggers and lead to LOT involves IL-15 upregulation. This cytokine was shown to induce LOT^{106,173} and to be upregulated upon stimulation with lipopolysaccharide or double-stranded RNA¹⁷⁴. Interestingly, IL-15 is not implicated in reovirus-mediated LOT⁵, suggesting that it can constitute an independent inflammatory pathway leading to LOT. More specifically, IL-15 was shown in mice to endow RA with adjuvant properties and induce the differentiation of intestinal CD103⁺ DCs with a pro-inflammatory phenotype that produce high levels of IL-12 (REF.¹⁰⁶). Consequently, upregulation of IL-15 in the lamina propria blocks pT_{reg} cell differentiation and induces T_H1 cell responses to dietary antigens^{106,173}. These findings are relevant to coeliac disease¹⁷³, in which polymorphisms in the gene encoding IL-12 are suggested to be a genetic risk factor^{175–177} and in which IL-15 upregulation in the lamina propria^{178–180} is associated with an upregulation of IL-12 (REF.¹⁰⁶) according to experimental evidence.

In summary, multiple factors have to be considered to define the exact underlying mechanisms of how enteric virus or bacterial infections affect CD103⁺CD11b[−] DCs, other

DC subsets and mucosal myeloid cells, such as by altering the RALDH2 activity of CD103⁺CD11b⁻ DCs, suppressing the tolerogenic programme or inducing a transcription factor that regulates the pro-inflammatory programme in these cells.

Mechanisms in T helper 2 cell-mediated food allergy.

The stimulation of IECs by pathogens (such as helminths) and PAMPs (such as bacterial TLR2 ligands) results in the production of thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which consequently disrupts barrier integrity and leads to T_H2 cell immunity^{181,182} (FIG. 3). A population of small intestinal CD103⁺CD11b⁺ DCs were shown to mediate mucosal T_H2 cell responses against parasites in mice, and it was also shown that IRF4 is involved and dependent on the type of microbial trigger¹⁸³. Indications exist that certain helminth infections such as those with *Heligmosomoides polygyrus* can suppress food allergy via a mechanism requiring IL-10 that in a dominant manner can suppress T_H2 cell responses^{184,185}; however, precise mechanisms are lacking. In general, the helminth-elicited T_H2 cell response is characterized by high levels of systemic helminth-induced IgE and IgG1 (REF.¹⁸⁶) and by the production of a series of inflammatory mediators, such as histamine and cytokines (including IL-4, IL-13, IL-6 and TNF), which are released from degranulating mast cells and can further impair intestinal barrier function¹³⁹. Accordingly, *Candida albicans* colonization was shown to promote gastrointestinal permeation of oral antigens, which was in part mediated by mucosal infiltration and degranulation of mast cells in mice¹⁸⁷. Future studies are required to clearly define the microbial-triggered T_H2 cell immune response that leads to food allergy.

Conclusions

Development of immune tolerance to dietary antigens is key for homeostatic intestinal and systemic immune responses. Investigations on the role of microbial determinants in preventing or leading to hypersensitivity reactions to innocuous dietary antigens have been intensively performed during the past two decades. Depletion of protective bacterial strains from the gut microbiota with beneficial metabolic function or the presence of viral infections or bacterial opportunistic pathogens could affect the risk of developing food sensitivities through a variety of mechanisms. Genetic predisposition will probably influence the manner in which the host responds to these environmental pressures. The best understood mechanisms involve indirect effects by bacterial metabolites and modification of antigenicity of dietary substrates and direct host effects that impair T_{reg} cell responses or imprint a pro-inflammatory programme in the host. Although there is currently great emphasis on dietary modulation of the gut microbiota to improve health, this area requires more mechanistic evidence (BOX 1). Deep knowledge of specific micro-organism–diet interactions and their underlying molecular pathways will be necessary to develop prevention and novel therapies to treat food sensitivities.

Acknowledgements

E.F.V. is funded by Canadian Institute of Health Research grant MOP#142773 and holds a Canada Research Chair in Microbiota, Inflammation and Nutrition. A.C. holds a fellowship award from the Farncombe Family. M.M. was awarded a Crohn's & Colitis Foundation of America Research fellowship award (ID: 480735). B.J. is funded by

grants R01DK098435, R01DK100619 and R01DK067180 and by Digestive Diseases Research Core Center grant P30 DK42086. The authors thank R. Hinterleitner for critically editing the Review.

References

1. Turnbull JL, Adams HN & Gorard DA Review article: the diagnosis and management of food allergy and food intolerances. *Aliment. Pharmacol. Ther.* 41, 3–25 (2015). [PubMed: 25316115]
 2. Rubio-Tapia A. et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* 137, 88–93 (2009). [PubMed: 19362553]
 3. Tang ML & Mullins RJ Food allergy: is prevalence increasing? *Internal Med. J.* 47, 256–261 (2017). [PubMed: 28260260]
 4. Verdu EF, Galipeau HJ & Jabri B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat. Rev. Gastroenterol. Hepatol.* 12, 497–506 (2015). [PubMed: 26055247]
 5. Bouziat R. et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* 356, 44–50 (2017).
- This study provides support for the concept that viruses can disrupt intestinal immune homeostasis and initiate loss of oral tolerance and T helper 1 cell immunity to dietary antigen.
- [PubMed: 28386004]
6. Caminero A. et al. Duodenal bacteria from patients with celiac disease and healthy subjects distinctly affect gluten breakdown and immunogenicity. *Gastroenterology* 151, 670–683 (2016).
- This study shows that the intestinal microbiota has a dual effect in gluten metabolism in vivo, increasing or reducing gluten immunogenicity.
- [PubMed: 27373514]
7. Smith PM et al. The microbial metabolites, short-chain fatty acids, regulate colonic T_{reg} cell homeostasis. *Science* 341, 569–573 (2013). [PubMed: 23828891]
 8. McCarville JL, Caminero A. & Verdu EF Novel perspectives on therapeutic modulation of the gut microbiota. *Ther. Adv. Gastroenterol.* 9, 580–593 (2016).
 9. Lomer MC, Parkes GC & Sanderson JD Review article: lactose intolerance in clinical practice — myths and realities. *Aliment. Pharmacol. Ther.* 27, 93–103 (2008). [PubMed: 17956597]
 10. Saito YA, Locke GR 3rd, Weaver AL, Zinsmeister AR & Talley NJ Diet and functional gastrointestinal disorders: a population-based case-control study. *Am. J. Gastroenterol.* 100, 2743–2748 (2005). [PubMed: 16393229]
 11. Moayyedi P. et al. The effect of dietary intervention on irritable bowel syndrome: a systematic review. *Clin. Transl Gastroenterol.* 6, e107 (2015). [PubMed: 26291435]
 12. Shepherd SJ, Parker FC, Muir JG & Gibson PR Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin. Gastroenterol. Hepatol.* 6, 765–771 (2008). [PubMed: 18456565]
 13. Teufel M. et al. Psychological burden of food allergy. *World J. Gastroenterol.* 13, 3456–3465 (2007). [PubMed: 17659692]
 14. Sicherer SH Food allergy. *Lancet* 360, 701–710 (2002). [PubMed: 12241890]
 15. Morita H, Nomura I, Matsuda A, Saito H. & Matsumoto K. Gastrointestinal food allergy in infants. *Allergol Int.* 62, 297–307 (2013). [PubMed: 23974876]
 16. Sicherer SH & Sampson HA Food allergy: recent advances in pathophysiology and treatment. *Annu. Rev. Med.* 60, 261–277 (2009). [PubMed: 18729729]
 17. Sampson HA & Anderson JA Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J. Pediatr. Gastroenterol. Nutr.* 30, S87–S94 (2000). [PubMed: 10634304]
 18. Ludvigsson JF et al. The Oslo definitions for coeliac disease and related terms. *Gut* 62, 43–52 (2013). [PubMed: 22345659]

19. Schuppan D, Pickert G, Ashfaq-Khan M. & Zevallos V. Non-celiac wheat sensitivity: differential diagnosis, triggers and implications. *Best Pract. Res. Clin. Gastroenterol.* 29, 469–476 (2015). [PubMed: 26060111]
20. DiGiacomo DV, Tennyson CA, Green PH & Demmer RT Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009–2010. *Scand. J. Gastroenterol.* 48, 921–925 (2013). [PubMed: 23834276]
21. Aziz I. et al. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *Eur. J. Gastroenterol. Hepatol.* 26, 33–39 (2014). [PubMed: 24216570]
22. Kaukinen K. et al. Intolerance to cereals is not specific for coeliac disease. *Scand. J. Gastroenterol.* 35, 942–946 (2000). [PubMed: 11063153]
23. Tanpowpong P. et al. Coeliac disease and gluten avoidance in New Zealand children. *Arch. Dis. Childhood* 97, 12–16 (2012). [PubMed: 22075107]
24. Lebwohl B, Ludvigsson JF & Green PH Celiac disease and non-celiac gluten sensitivity. *BMJ* 351, h4347 (2015).
25. Verbeke K. Nonceliac gluten sensitivity: what is the culprit? *Gastroenterology* 154, 471–473 (2018). [PubMed: 29337156]
26. Skodje GI et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology* 154, 529–539 (2018). [PubMed: 29102613]
27. Junker Y. et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J. Exp. Med.* 209, 2395–2408 (2012). [PubMed: 23209313]
28. Zevallos VF et al. Nutritional wheat amylase-trypsin inhibitors promote intestinal inflammation via activation of myeloid cells. *Gastroenterology* 152, 1100–1113 (2017). [PubMed: 27993525]
29. Prescott SL et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organiz. J.* 6, 21 (2013).
30. Osborne NJ et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J. Allergy Clin. Immunol.* 127, 668–676 (2011). [PubMed: 21377036]
31. Wang J. & Sampson HA Food allergy. *J. Clin. Invest.* 121, 827–835 (2011). [PubMed: 21364287]
32. Singh P. et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* 16, 823–836.e2 (2018). [PubMed: 29551598]
33. Pozo-Rubio T. et al. Influence of breastfeeding versus formula feeding on lymphocyte subsets in infants at risk of coeliac disease: the PROFICEL study. *Eur. J. Nutr.* 52, 637–646 (2013). [PubMed: 22576041]
34. Kempainen KM et al. Factors that increase risk of celiac disease autoimmunity after a gastrointestinal infection in early life. *Clin. Gastroenterol. Hepatol.* 15, 694–702 (2017). [PubMed: 27840181]
35. Szajewska H. et al. Gluten introduction and the risk of coeliac disease: a position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J. Pediatr. Gastroenterol. Nutr.* 62, 507–513 (2016). [PubMed: 26815017]
36. Decker E. et al. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. *Pediatrics* 125, e1433–1440 (2010). [PubMed: 20478942]
37. Marild K. et al. Antibiotic exposure and the development of coeliac disease: a nationwide case-control study. *BMC Gastroenterol.* 13, 109 (2013). [PubMed: 23834758]
38. Bashir ME, Louie S, Shi HN & Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *J. Immunol.* 172, 6978–6987 (2004). [PubMed: 15153518]
39. Crespo-Escobar P. et al. The role of gluten consumption at an early age in celiac disease development: a further analysis of the prospective PreventCD cohort study. *Am. J. Clin. Nutr.* 105, 890–896 (2017). [PubMed: 28228423]
40. Uusitalo U. et al. Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort. *Am. J. Clin. Nutr.* 102, 1216–1221 (2015). [PubMed: 26447157]

41. Stene LC et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am. J. Gastroenterol.* 101, 2333–2340 (2006). [PubMed: 17032199]
42. Marild K, Kahrs CR, Tapia G, Stene LC & Stordal K. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *Am. J. Gastroenterol.* 110, 1475–1484 (2015). [PubMed: 26346866]
43. Plot L. & Amital H. Infectious associations of Celiac disease. *Autoimmun. Rev.* 8, 316–319 (2009). [PubMed: 18973831]
44. Cheung DS & Grayson MH Role of viruses in the development of atopic disease in pediatric patients. *Curr. Allergy Asthma Rep.* 12, 613–620 (2012). [PubMed: 22911226]
45. Verdu EF, Mauro M, Bourgeois J. & Armstrong D. Clinical onset of celiac disease after an episode of *Campylobacter jejuni* enteritis. *Can. J. Gastroenterol.* 21, 453–455 (2007). [PubMed: 17637949]
46. Kagnoff MF, Austin RK, Hubert JJ, Bernardin JE & Kasarda DD Possible role for a human adenovirus in the pathogenesis of celiac disease. *J. Exp. Med.* 160, 1544–1557 (1984). [PubMed: 6491604]
47. Abadie V, Sollid LM, Barreiro LB & Jabri B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu. Rev. Immunol.* 29, 493–525 (2011). [PubMed: 21219178]
48. Shi HN, Liu HY & Nagler-Anderson C. Enteric infection acts as an adjuvant for the response to a model food antigen. *J. Immunol.* 165, 6174–6182 (2000). [PubMed: 11086051]
49. Honeyman MC et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* 49, 1319–1324 (2000). [PubMed: 10923632]
50. Silvester JA & Leffler DA Is autoimmunity infectious? The effect of gastrointestinal viral infections and vaccination on risk of celiac disease autoimmunity. *Clin. Gastroenterol. Hepatol.* 15, 703–705 (2017). [PubMed: 28017844]
51. Vaarala O, Jokinen J, Lahdenkari M. & Leino T. Rotavirus vaccination and the risk of celiac disease or type 1 diabetes in Finnish children at early life. *Pediatr. Infect. Dis. J.* 36, 674–675 (2017).
52. Karhus LL et al. Influenza and risk of later celiac disease: a cohort study of 2.6 million people. *Scand. J. Gastroenterol.* 53, 15–23 (2018). [PubMed: 29076383]
53. Garg A, Reddy C, Duseja A, Chawla Y. & Dhiman RK Association between celiac disease and chronic hepatitis c virus infection. *J. Clin. Exp. Hepatol.* 1, 41–44 (2011). [PubMed: 25755310]
54. Nadal I, Donat E, Ribes-Koninckx C, Calabuig M. & Sanz Y. Imbalance in the composition of the duodenal microbiota of children with coeliac disease. *J. Med. Microbiol.* 56, 1669–1674 (2007). [PubMed: 18033837]
55. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M. & Sanz Y. Imbalances in faecal and duodenal *Bifidobacterium* species composition in active and non-active coeliac disease. *BMC Microbiol.* 8, 232 (2008). [PubMed: 19102766]
56. Nistal E. et al. Differences of small intestinal bacteria populations in adults and children with/ without celiac disease: effect of age, gluten diet, and disease. *Inflammatory Bowel Diseases* 18, 649–656 (2012). [PubMed: 21826768]
57. Nistal E. et al. Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. *Biochimie* 94, 1724–1729 (2012). [PubMed: 22542995]
58. Wacklin P. et al. Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. *Am. J. Gastroenterol.* 109, 1933–1941 (2014). [PubMed: 25403367]
59. D'Argenio V. et al. Metagenomics reveals dysbiosis and a potentially pathogenic *N. flavescens* strain in duodenum of adult celiac patients. *Am. J. Gastroenterol.* 111, 879–890 (2016). [PubMed: 27045926]
60. Azad MB et al. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin. Exp. Allergy* 45, 632–643 (2015). [PubMed: 25599982]
61. Abrahamsson TR et al. Low diversity of the gut microbiota in infants with atopic eczema. *J. Allergy Clin. Immunol.* 129, 434–440 (2012). [PubMed: 22153774]

62. Hua X, Goedert JJ, Pu A, Yu G. & Shi J. Allergy associations with the adult fecal microbiota: analysis of the American Gut Project. *EBioMedicine* 3, 172–179 (2016). [PubMed: 26870828]
 63. Sanz Y, De Pama G. & Laparra M. Unraveling the ties between celiac disease and intestinal microbiota. *Int. Rev. Immunol.* 30, 207–218 (2011). [PubMed: 21787226]
 64. Palma GD et al. Influence of milk-feeding type and genetic risk of developing coeliac disease on intestinal microbiota of infants: the PROFICEL study. *PLoS ONE* 7, e30791 (2012).
 65. Bunyavanich S. et al. Early-life gut microbiome composition and milk allergy resolution. *J. Allergy Clin. Immunol.* 138, 1122–1130 (2016). [PubMed: 27292825]
 66. Ling Z. et al. Altered fecal microbiota composition associated with food allergy in infants. *Appl. Environ. Microbiol.* 80, 2546–2554 (2014). [PubMed: 24532064]
 67. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M. & Sanz Y. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *J. Clin. Pathol.* 62, 264–269 (2009). [PubMed: 18996905]
 68. Galipeau HJ et al. Intestinal microbiota modulates gluten-induced immunopathology in humanized mice. *Am. J. Pathol.* 185, 2969–2982 (2015).
- This study shows that the intestinal microbiota can both positively and negatively modulate gluten-induced immunopathology in mice.
- [PubMed: 26456581]
69. 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* 14, 559–570 (2013). [PubMed: 24237701]
 70. Noval Rivas M. et al. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. *J. Allergy Clin. Immunol.* 131, 201–212 (2013). [PubMed: 23201093]
 71. Atarashi K. et al. T_{reg} induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 500, 232–236 (2013). [PubMed: 23842501]
 72. Stefká AT et al. Commensal bacteria protect against food allergen sensitization. *Proc. Natl Acad. Sci. USA* 111, 13145–13150 (2014).
- In this study, selective colonization of gnotobiotic mice is used to demonstrate that the allergy-protective capacity is contained within the Clostridia class. Clostridia members induce IL-22 production, reducing uptake of orally administered dietary antigen into the systemic circulation and contributing to protection against food sensitization.
- [PubMed: 25157157]
73. Atarashi K. et al. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 331, 337–341 (2011). [PubMed: 21205640]
 74. Wu GD et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334, 105–108 (2011). [PubMed: 21885731]
 75. David LA et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505, 559–563 (2014). [PubMed: 24336217]
 76. Lee D. et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 148, 1087–1106 (2015). [PubMed: 25597840]
 77. Sonnenburg JL & Backhed F. Diet-microbiota interactions as moderators of human metabolism. *Nature* 535, 56–64 (2016). [PubMed: 27383980]
 78. Gourbeyre P. et al. Perinatal and postweaning exposure to galactooligosaccharides/inulin prebiotics induced biomarkers linked to tolerance mechanism in a mouse model of strong allergic sensitization. *J. Agric. Food Chem.* 61, 6311–6320 (2013). [PubMed: 23746232]
 79. Kunisawa J. et al. Dietary omega3 fatty acid exerts anti-allergic effect through the conversion to 17,18-epoxyeicosatetraenoic acid in the gut. *Sci. Rep.* 5, 9750 (2015). [PubMed: 26065911]
 80. Hamer HM et al. Review article: the role of butyrate on colonic function. *Aliment. Pharmacol. Ther.* 27, 104–119 (2008). [PubMed: 17973645]

81. Koppel N, Maini Rekdal V. & Balskus EP Chemical transformation of xenobiotics by the human gut microbiota. *Science* 356, eaag2770 (2017).
 82. Shan L. et al. Structural basis for gluten intolerance in celiac sprue. *Science* 297, 2275–2279 (2002). [PubMed: 12351792]
 83. Sollid LM & Jabri B. Triggers and drivers of autoimmunity: lessons from coeliac disease. *Nat. Rev. Immunology* 13, 294–302 (2013). [PubMed: 23493116]
 84. Caminero A. et al. Diversity of the cultivable human gut microbiome involved in gluten metabolism: isolation of microorganisms with potential interest for coeliac disease. *FEMS Microbiol. Ecol.* 88, 309–319 (2014). [PubMed: 24499426]
 85. Caminero A. et al. Differences in gluten metabolism among healthy volunteers, coeliac disease patients and first-degree relatives. *Br. J. Nutr.* 114, 1157–1167 (2015). [PubMed: 26428276]
 86. Herran AR et al. Gluten-degrading bacteria are present in the human small intestine of healthy volunteers and celiac patients. *Res. Microbiol.* 168, 673–684 (2017). [PubMed: 28526528]
 87. Helmerhorst EJ, Zamakhchari M, Schuppan D. & Oppenheim FG Discovery of a novel and rich source of gluten-degrading microbial enzymes in the oral cavity. *PLoS ONE* 5, e13264 (2010).
 88. Fernandez-Feo M. et al. The cultivable human oral gluten-degrading microbiome and its potential implications in coeliac disease and gluten sensitivity. *Clin. Microbiol. Infect.* 19, E386–E394 (2013). [PubMed: 23714165]
 89. Nistal E. et al. Study of duodenal bacterial communities by 16s rRNA gene analysis in adults with active celiac disease versus non celiac disease controls. *J. Appl. Microbiol.* 120, 1691–1700 (2016). [PubMed: 26913982]
 90. Borton MA et al. Chemical and pathogen-induced inflammation disrupt the murine intestinal microbiome. *Microbiome* 5, 47 (2017). [PubMed: 28449706]
 91. Dieterich W. et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat. Med.* 3, 797–801 (1997). [PubMed: 9212111]
 92. Zhou L. et al. Abrogation of immunogenic properties of gliadin peptides through transamidation by microbial transglutaminase is acyl-acceptor dependent. *J. Agric. Food Chem.* 65, 7542–7552 (2017). [PubMed: 28771001]
 93. Toomer OT, Do A, Pereira M. & Williams K. Effect of simulated gastric and intestinal digestion on temporal stability and immunoreactivity of peanut, almond, and pine nut protein allergens. *J. Agric. Food Chem.* 61, 5903–5913 (2013). [PubMed: 23742710]
 94. Tye-Din JA et al. Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease. *Sci. Transl. Med.* 2, 41ra51 (2010).
 95. Maynard CL, Elson CO, Hatton RD & Weaver CT Reciprocal interactions of the intestinal microbiota and immune system. *Nature* 489, 231–241 (2012). [PubMed: 22972296]
 96. Morrison DJ & Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 7, 189–200 (2016). [PubMed: 26963409]
 97. Lamas B. et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat. Med.* 22, 598–605 (2016). [PubMed: 27158904]
 98. Tjellstrom B. et al. Gut microflora associated characteristics in children with celiac disease. *Am. J. Gastroenterol.* 100, 2784–2788 (2005). [PubMed: 16393236]
 99. Brestoff JR & Artis D. Commensal bacteria at the interface of host metabolism and the immune system. *Nature Immunol.* 14, 676–684 (2013). [PubMed: 23778795]
 100. Arpaia N. et al. Metabolites produced by commensal bacteria promote peripheral regulatory T cell generation. *Nature* 504, 451–455 (2013).
- This study shows that bacterial metabolites such as short-chain fatty acids mediate communication between the commensal microbiota and the immune system, affecting the balance between pro-inflammatory and anti-inflammatory mechanisms.
- [PubMed: 24226773]
101. Furusawa Y. et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 504, 446–450 (2013). [PubMed: 24226770]

102. Hadis U. et al. Intestinal tolerance requires gut homing and expansion of FoxP3⁺ regulatory T cells in the lamina propria. *Immunity* 34, 237–246 (2011). [PubMed: 21333554]
103. Bilate AM & Lafaille JJ Induced CD4⁺Foxp3⁺ regulatory T cells in immune tolerance. *Annu. Rev. Immunol.* 30, 733–758 (2012). [PubMed: 22224762]
104. Tan J. et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. *Cell Rep.* 15, 2809–2824 (2016).
- This study finds that dietary elements, including fibre and vitamin A, are essential for the tolerogenic function of CD103⁺ dendritic cells and the maintenance of mucosal homeostasis, including proper IgA responses and epithelial barrier function. The practical outcome of this study is the promotion of oral tolerance and protection from food allergy.
- [PubMed: 27332875]
105. Fukuda S. et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 469, 543–547 (2011). [PubMed: 21270894]
106. DePaolo RW et al. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. *Nature* 471, 220–224 (2011).
- This study finds that, in conjunction with IL-15, retinoic acid rapidly activates dendritic cells to release pro-inflammatory cytokines, and as a result, in a stressed intestinal environment, retinoic acid acts as an adjuvant that promotes rather than prevents inflammatory cellular and humoral responses to fed antigens.
- [PubMed: 21307853]
107. Meisel M. et al. Interleukin-15 promotes intestinal dysbiosis with butyrate deficiency associated with increased susceptibility to colitis. *ISME J.* 11, 15–30 (2017). [PubMed: 27648810]
108. Berni Canani R. et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. *ISME J.* 10, 742–750 (2016). [PubMed: 26394008]
109. Zelante T. et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* 39, 372–385 (2013). [PubMed: 23973224]
110. Nguyen NT et al. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. *Proc. Natl Acad. Sci. USA* 107, 19961–19966 (2010). [PubMed: 21041655]
111. Schulz VJ et al. Aryl hydrocarbon receptor activation affects the dendritic cell phenotype and function during allergic sensitization. *Immunobiology* 218, 1055–1062 (2013). [PubMed: 23433705]
112. Hammerschmidt-Kamper C. et al. Indole-3-carbinol, a plant nutrient and AhR-Ligand precursor, supports oral tolerance against OVA and improves peanut allergy symptoms in mice. *PLoS ONE* 12, e0180321 (2017).
113. Schulz VJ, Smit JJ & Pieters RH The aryl hydrocarbon receptor and food allergy. *Vet. Q.* 33, 94–107 (2013). [PubMed: 23745732]
114. Mazmanian SK, Round JL & Kasper DL A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453, 620–625 (2008). [PubMed: 18509436]
115. Atarashi K. & Honda K. Microbiota in autoimmunity and tolerance. *Curr. Opin. Immunol.* 23, 761–768 (2011). [PubMed: 22115876]
116. Round JL & Mazmanian SK Inducible Foxp3⁺ regulatory T cell development by a commensal bacterium of the intestinal microbiota. *Proc. Natl Acad. Sci. USA* 107, 12204–12209 (2010).
- Here, the immunomodulatory molecule polysaccharide A of *Bacteroides fragilis* is shown to mediate the conversion of CD4⁺ T cells into FOXP3⁺ regulatory T cells that produce IL-10 during commensal colonization. *B. fragilis* co-opts the regulatory T cell lineage differentiation pathway in the gut to actively induce mucosal tolerance.

[PubMed: 20566854]

117. Cerf-Bensussan N. & Gaboriau-Routhiau V. The immune system and the gut microbiota: friends or foes? *Nat. Rev Immunology* 10, 735–744 (2010). [PubMed: 20865020]
118. Hrnčir T, Stepankova R, Kozakova H, Hudcovic T. & Tlaskalova-Hogenova H. Gut microbiota and lipopolysaccharide content of the diet influence development of regulatory T cells: studies in germ-free mice. *BMC Immunol.* 9, 65 (2008). [PubMed: 18990206]
119. Schwarzer M. et al. Diet matters: endotoxin in the diet impacts the level of allergic sensitization in germ-free mice. *PLoS ONE* 12, e0167786 (2017).
120. Olivares M, Castillejo G, Varea V. & Sanz Y. Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of *Bifidobacterium longum* CECT 7347 in children with newly diagnosed coeliac disease. *Br. J. Nutr.* 112, 30–40 (2014). [PubMed: 24774670]
121. Pinto-Sanchez MI et al. *Bifidobacterium infantis* NLS super strain reduces the expression of α -defensin-5, a marker of innate immunity, in the mucosa of active celiac disease patients. *J. Clin. Gastroenterol.* 51, 814–817 (2017). [PubMed: 27636409]
122. Enomoto T. et al. Effects of bifidobacterial supplementation to pregnant women and infants in the prevention of allergy development in infants and on fecal microbiota. *Allergol. Int.* 63, 575–585 (2014). [PubMed: 25056226]
123. Hill DA et al. Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. *Nat. Med.* 18, 538–546 (2012). [PubMed: 22447074]
124. De Angelis M. et al. VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for celiac sprue. *Biochim. Biophys. Acta* 1762, 80–93 (2006). [PubMed: 16311022]
125. Schiavi E. et al. Oral therapeutic administration of a probiotic mixture suppresses established Th2 responses and systemic anaphylaxis in a murine model of food allergy. *Allergy* 66, 499–508 (2011). [PubMed: 21058959]
126. Barletta B. et al. Probiotic VSL#3-induced TGF- β ameliorates food allergy inflammation in a mouse model of peanut sensitization through the induction of regulatory T cells in the gut mucosa. *Mol. Nutr. Food Res.* 57, 2233–2244 (2013). [PubMed: 23943347]
127. McCarville JL et al. A commensal *Bifidobacterium longum* strain improves gluten-related immunopathology in mice through expression of a serine protease inhibitor. *Appl. Environ. Microbiol.* 10.1128/AEM.01323-17 (2017).
128. Galipeau HJ et al. Novel role of the serine protease inhibitor elafin in gluten-related disorders. *Am. J. Gastroenterol.* 109, 748–756 (2014). [PubMed: 24710505]
129. Kim JH et al. Extracellular vesicle-derived protein from *Bifidobacterium longum* alleviates food allergy through mast cell suppression. *J. Allergy Clin. Immunol.* 137, 507–516 (2016). [PubMed: 26433560]
130. Tang ML et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J. Allergy Clin. Immunol.* 135, 737–744 (2015). [PubMed: 25592987]
131. Wood RA et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy* 68, 803–808 (2013). [PubMed: 23621498]
132. Pabst O. & Mowat AM Oral tolerance to food protein. *Mucosal Immunol.* 5, 232–239 (2012). [PubMed: 22318493]
133. Faria AM & Weiner HL Oral tolerance. *Immunol. Rev.* 206, 232–259 (2005). [PubMed: 16048553]
134. Fasano A. & Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 2, 416–422 (2005). [PubMed: 16265432]
135. Menard S, Cerf-Bensussan N. & Heyman M. Multiple facets of intestinal permeability and epithelial handling of dietary antigens. *Mucosal Immunol.* 3, 247–259 (2010). [PubMed: 20404811]
136. Berin MC & Sampson HA Mucosal immunology of food allergy. *Curr. Biol.* 23, R389–R400 (2013). [PubMed: 23660362]

137. Koning F, Schuppan D, Cerf-Bensussan N. & Sollid LM Pathomechanisms in celiac disease. *Best Pract. Res. Clin. Gastroenterol.* 19, 373–387 (2005). [PubMed: 15925843]
 138. Vogelsang H, Schwarzenhofer M. & Oberhuber G. Changes in gastrointestinal permeability in celiac disease. *Dig. Dis.* 16, 333–336 (1998). [PubMed: 10207217]
 139. Perrier C. & Corthesy B. Gut permeability and food allergies. *Clin. Exp. Allergy* 41, 20–28 (2011). [PubMed: 21070397]
 140. Amieva MR et al. Disruption of the epithelial apical-junctional complex by *Helicobacter pylori* CagA. *Science* 300, 1430–1434 (2003). [PubMed: 12775840]
 141. Wu Z, Nybom P. & Magnusson KE Distinct effects of *Vibrio cholerae* haemagglutinin/protease on the structure and localization of the tight junction-associated proteins occludin and ZO-1. *Cell. Microbiol.* 2, 11–17 (2000). [PubMed: 11207559]
 142. Maharshak N. et al. *Enterococcus faecalis* gelatinase mediates intestinal permeability via protease-activated receptor 2. *Infection Immun.* 83, 2762–2770 (2015).
 143. Steck N. et al. *Enterococcus faecalis* metalloprotease compromises epithelial barrier and contributes to intestinal inflammation. *Gastroenterology* 141, 959–971 (2011). [PubMed: 21699778]
 144. Ng KM et al. Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. *Nature* 502, 96–99 (2013). [PubMed: 23995682]
 145. Rescigno M. & Di Sabatino A. Dendritic cells in intestinal homeostasis and disease. *J. Clin. Invest.* 199, 2441–2450 (2009).
 146. Esterhazy D. et al. Classical dendritic cells are required for dietary antigen-mediated induction of peripheral T_{reg} cells and tolerance. *Nat. Immunol.* 17, 545–555 (2016).
- This study finds that classic dendritic cells are critical for peripherally induced regulatory T cell induction and oral tolerance.
- [PubMed: 27019226]
147. Wells JM, Rossi O, Meijerink M. & van Baarlen P. Epithelial crosstalk at the microbiota-mucosal interface. *Proc. Natl Acad. Sci. USA* 108 (Suppl. 1), 4607–4614 (2011). [PubMed: 20826446]
 148. Coleman OI & Haller D. Bacterial signaling at the intestinal epithelial interface in inflammation and cancer. *Frontiers Immunol.* 8, 1927 (2017).
 149. Araya RE et al. Mechanisms of innate immune activation by gluten peptide p31–43 in mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* 311, G40–49 (2016). [PubMed: 27151946]
 150. Biswas A. et al. Negative regulation of Toll-like receptor signaling plays an essential role in homeostasis of the intestine. *Eur. J. Immunol.* 41, 182–194 (2011). [PubMed: 21182089]
 151. Medvedev AE Toll-like receptor polymorphisms, inflammatory and infectious diseases, allergies, and cancer. *J. Interferon Cytokine Res.* 33, 467–484 (2013). [PubMed: 23675778]
 152. Miedema KG et al. Polymorphisms in the TLR6 gene associated with the inverse association between childhood acute lymphoblastic leukemia and atopic disease. *Leukemia* 26, 1203–1210 (2012). [PubMed: 22134717]
 153. Cheng J. et al. Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease. *BMC Gastroenterol.* 13, 113 (2013). [PubMed: 23844808]
 154. Marafini I. et al. TNF- α producing innate lymphoid cells (ILCs) are increased in active celiac disease and contribute to promote intestinal atrophy in mice. *PLoS ONE* 10, e0126291 (2015).
 155. Burton OT et al. IgE promotes type 2 innate lymphoid cells in murine food allergy. *Clin. Exp. Allergy* 48, 288–296 (2017).
 156. Di Liberto D. et al. Predominance of type 1 innate lymphoid cells in the rectal mucosa of patients with non-celiac wheat sensitivity: reversal after a wheat-free diet. *Clin. Transl Gastroenterol.* 7, e178 (2016). [PubMed: 27388423]
 157. Chu DK et al. T helper cell IL-4 drives intestinal Th2 priming to oral peanut antigen, under the control of OX40L and independent of innate-like lymphocytes. *Mucosal Immunol.* 7, 1395–1404 (2014). [PubMed: 24781052]

158. Lee JB et al. IL-25 and CD4⁺ TH2 cells enhance type 2 innate lymphoid cell-derived IL-13 production, which promotes IgE-mediated experimental food allergy. *J. Allergy Clin. Immunol.* 137, 1216–1225 (2016). [PubMed: 26560039]
159. Artis D. & Spits H. The biology of innate lymphoid cells. *Nature* 517, 293–301 (2015). [PubMed: 25592534]
160. Mortha A. et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science* 343, 1249288 (2014).
161. Chua HH et al. Intestinal dysbiosis featuring abundance of *Ruminococcus gnavus* associates with allergic diseases in infants. *Gastroenterology* 154, 154–167 (2018). [PubMed: 28912020]
162. Gerbe F. et al. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* 529, 226–230 (2016). [PubMed: 26762460]
163. Coombes JL et al. A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF- β and retinoic acid-dependent mechanism. *J. Exp. Med.* 204, 1757–1764 (2007). [PubMed: 17620361]
164. Sun CM et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J. Exp. Med.* 204, 1775–1785 (2007). [PubMed: 17620362]
165. Hall JA, Grainger JR, Spencer SP & Belkaid Y. The role of retinoic acid in tolerance and immunity. *Immunity* 35, 13–22 (2011). [PubMed: 21777796]
166. Martinez-Lopez M, Iborra S, Conde-Garrosa R. & Sancho D. Batf3-dependent CD103⁺ dendritic cells are major producers of IL-12 that drive local Th1 immunity against *Leishmania* major infection in mice. *Eur. J. Immunol.* 45, 119–129 (2015). [PubMed: 25312824]
167. Luda KM et al. IRF8 transcription-factor-dependent classical dendritic cells are essential for intestinal T cell homeostasis. *Immunity* 44, 860–874 (2016). [PubMed: 27067057]
168. Laffont S, Siddiqui KR & Powrie F. Intestinal inflammation abrogates the tolerogenic properties of MLN CD103⁺ dendritic cells. *Eur. J. Immunol.* 40, 1877–1883 (2010). [PubMed: 20432234]
169. Moretto MM, Harrow DI, Hawley TS & Khan IA Interleukin-12-producing CD103⁺CD11b⁺CD8⁺ dendritic cells are responsible for eliciting gut intraepithelial lymphocyte response against *Encephalitozoon cuniculi*. *Infection Immun.* 83, 4719–4730 (2015).
170. Di Sabatino A. et al. Evidence for the role of interferon- α production by dendritic cells in the Th1 response in celiac disease. *Gastroenterology* 133, 1175–1187 (2007). [PubMed: 17919493]
171. Jabri B. & Sollid LM Tissue-mediated control of immunopathology in coeliac disease. *Nat. Rev. Immunol.* 9, 858–870 (2009). [PubMed: 19935805]
172. Verdu EF & Caminero A. How infection can incite sensitivity to food. *Science* 356, 29–30 (2017). [PubMed: 28385972]
173. Abadie V. & Jabri B. IL-15: a central regulator of celiac disease immunopathology. *Immunol. Rev.* 260, 221–234 (2014). [PubMed: 24942692]
174. Mattei F, Schiavoni G, Belardelli F. & Tough DF IL-15 is expressed by dendritic cells in response to type I IFN, double-stranded RNA, or lipopolysaccharide and promotes dendritic cell activation. *J. Immunol.* 167, 1179–1187 (2001). [PubMed: 11466332]
175. Hunt KA et al. Newly identified genetic risk variants for celiac disease related to the immune response. *Nature Genet.* 40, 395–402 (2008). [PubMed: 18311140]
176. Guo CC et al. Meta-analysis on associations of RGS1 and IL12A polymorphisms with celiac disease risk. *Int. J. Mol. Sci.* 17, 457 (2016). [PubMed: 27043536]
177. Zhernakova A. et al. Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection. *Am. J. Hum. Genet.* 86, 970–977 (2010). [PubMed: 20560212]
178. Green PH & Jabri B. Celiac disease and other precursors to small-bowel malignancy. *Gastroenterol. Clin. North Amer.* 31, 625–639 (2002). [PubMed: 12134621]
179. Mention JJ et al. Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology* 125, 730–745 (2003). [PubMed: 12949719]

180. Setty M. et al. Distinct and synergistic contributions of epithelial stress and adaptive immunity to functions of intraepithelial killer cells and active celiac disease. *Gastroenterology* 149, 681–691 (2015). [PubMed: 26001928]
181. Licona-Limon P, Kim LK, Palm NW & Flavell RA TH2, allergy and group 2 innate lymphoid cells. *Nature Immunol.* 14, 536–542 (2013). [PubMed: 23685824]
182. Khodoun MV, Tomar S, Tocker JE, Wang YH & Finkelman FD Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin, IL-25, and IL-33. *J. Allergy Clin. Immunol.* 141, 171–179 e171 (2018). [PubMed: 28552763]
183. Mayer JU et al. Different populations of CD11b+ dendritic cells drive Th2 responses in the small intestine and colon. *Nat. Commun.* 8, 15820 (2017). [PubMed: 28598427]
184. 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.* 169, 3284–3292 (2002). [PubMed: 12218148]
185. Ben-Ami Shor D, Harel M, Eliakim R. & Shoenfeld Y. The hygiene theory harnessing helminths and their ova to treat autoimmunity. *Clin. Rev. Allergy Immunol.* 45, 211–216 (2013). [PubMed: 23325330]
186. Hewitson JP, Grainger JR & Maizels RM Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. *Mol. Biochem. Parasitol.* 167, 1–11 (2009). [PubMed: 19406170]
187. Yamaguchi N. et al. Gastrointestinal *Candida* colonisation promotes sensitisation against food antigens by affecting the mucosal barrier in mice. *Gut* 55, 954–960 (2006).
- This study finds that *Candida* spp. colonization promotes sensitization against food antigens, at least partly owing to mast cell-mediated hyperpermeability in the gastrointestinal mucosa of mice.
- [PubMed: 16423887]

Outstanding questions in food sensitivities

- The identity of specific food triggers and the underlying mechanisms and biomarkers involved in the context of self-reported adverse food reactions in patients with functional gut disorders remain unclear.
- It is unknown whether intestinal dysbiosis in patients with food sensitivity is the consequence of ongoing (food-induced) inflammation or a post-infectious adverse effect that has a causal role in the breakdown of tolerance to antigen or allergen.
- It remains to be determined whether infections and increased gluten intake synergize to promote breakdown of tolerance to gluten in genetically susceptible people and whether there is a window of opportunity for this effect.
- The mechanisms underlying the paradoxically protective effect of certain helminths in food allergy remain unclear.

Key points

- The mechanisms underlying the expression of food sensitivities remain unclear; however, several studies demonstrate that gut microorganisms, along with other host predisposing factors, dictate the development of these conditions.
- Gut microorganisms can degrade or modify immunogenic food antigens or allergens, increasing or reducing their immunogenicity.
- Dietary food components that are insufficiently digested by host enzymes become bacterial substrates, leading to the production of metabolites such as short-chain fatty acids, which are involved in gut homeostasis.
- One key factor in the development of food sensitivities is intestinal barrier dysfunction, which can be influenced by gut microorganisms and pathogens through different pathways.
- Mucosal dendritic cells present dietary antigens to naive T helper cells, promoting their differentiation into peripheral T regulatory cells; virus-host interactions abrogate this response, inducing a pathogenic response to antigens.
- Enteric parasites induce T helper 2 cell immunity and protect against food allergy; this contradiction is explained by the observation that parasites induce IL-10, which blocks type 2 immunity.

Fig. 1 |. Classification of adverse reaction to food according to underlying pathophysiology.

Adverse reactions to food can be divided into food intolerances (non-immune mediated) and food sensitivities (immune mediated) according to their underlying pathophysiology. Both types can be subclassified into specific diseases on the basis of their pathophysiology. ATI, α -amylase-trypsin inhibitor; IgE, immunoglobulin E.

Fig. 2 |. Microbial metabolism in the pathogenesis of food sensitivities.

Dietary patterns constitute an important determinant of gut microbiota diversity, altering microbial community structure and metabolite production. Dietary food components that are not metabolized by the host become bacterial substrates. Products of bacterial metabolic activity, such as the short-chain fatty acids, are recognized by host receptors in dendritic cells (DCs) and epithelial cells promoting homeostasis through immune modulatory pathways and barrier protection (left side). Microorganisms can also metabolize food protein antigens through specific enzymatic activity, increasing or reducing their immunogenicity. Alteration of bacterial composition and/or the functional and metabolic capabilities of resident bacteria, as well as intestinal infections (microbial determinants), could promote T cell-mediated food sensitivities in genetically susceptible people (right side). A non-balanced diet can promote a microbiota with a lower diversity and metabolic output. The lack of bacterial metabolites could impair gut homeostasis, predisposing the host to develop food sensitivities. Dysbiosis could also lead to partially degraded food antigens, producing immunogenic peptides that translocate the mucosal barrier better than non-partially digested antigens. Once in the lamina propria, food antigens (such as gluten peptides) will be recognized by antigen-presenting cells such as DCs harbouring major histocompatibility

complex (MHC) class II genes, which mediate the production of pro-inflammatory cytokines (IL-12, IL-6 and IFN γ). In the case of coeliac disease, an adaptive immune response with gluten-specific T cells and B cells producing antibodies against gluten will be generated. TCR, T cell receptor.

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Fig. 3 |. Microorganisms can promote food sensitivities.

Under healthy conditions, short-chain fatty acid (SCFA)-producing bacteria help maintain oral tolerance to dietary antigens by reinforcing the intestinal epithelial cell (IEC) barrier to prevent uncontrolled pro-inflammatory host-responses. Normal barrier functions include immune and physical factors such as secretory immunoglobulin A (SIgA) and the expression of tight junction proteins (blue bars) that restrict mucosal access of both dietary and microbial antigens. The main antigen-sampling dendritic cells (DCs) are CD103⁺CD11b⁻ DCs that express retinal dehydrogenase 2 (RALDH2) and produce retinoic acid (RA) and that migrate to the mesenteric lymph nodes to promote the differentiation of naive CD4⁺ T cells into peripherally derived forkhead box protein P3 (FOXP3)⁺ regulator T (T_{reg}) cells (pT_{reg} cells) via a transforming growth factor-β (TGFβ)-dependent and RA-dependent mechanism. In the lamina propria, tolerogenic pT_{reg} cells suppress the inflammatory T cell response and mediate oral tolerance. Enteric pathogenic infections and dysbiosis can alter IEC barrier disruption, leading to uncontrolled translocation of dietary antigens, certain pathogens and pathogen-associated molecular patterns into the intestinal mucosa. Coeliac disease is characterized by a T helper 1 (T_H1) cell response to gluten that leads to IEC

destruction and villous atrophy. T_H1 cell responses in coeliac disease are linked to the differentiation of IL-12-producing and possibly IL-27-producing DCs. Most patients with coeliac disease display upregulation of pro-inflammatory IL-15, which can synergize with RA to induce DCs and promote T_H1 cell responses that then instruct plasma cells to produce anti-gluten and anti-transglutaminase 2 (TGase2) antibodies. Type 1 strain Lang (T1L) reovirus infection induces pro-inflammatory CD103⁺CD11b⁻ DCs that produce IL-12 via interferon regulatory factor 1 (IRF1) and block the differentiation of pT_{reg} cells. Food allergy is mediated by T_H2 cell responses to dietary antigens. IECs that produce thymic stromal lymphopoietin (TSLP) and IL-33, and tuft cells that produce IL-25, could contribute to food allergy by promoting differentiation of small intestinal CD103⁺CD11b⁺ DCs. Together with IgE-producing plasma cells, IL-4-producing basophils and the IgE-mediated degranulation of mast cells, these processes drive T_H2 cell immunity and consequently food allergy to dietary antigens. Microbial infections inducing IL-4, IL-5 and IL-13 could also contribute to promoting T_H2 cell responses to dietary antigens; however, the mechanisms remain to be defined. IL-13R, IL-13 receptor; IL-25R, IL-25 receptor (also known as IL-17RB); IL-33R, IL-33 receptor (also known as IL-1RL1); IL-4R, IL-4 receptor; MHC, major histocompatibility complex; TSLPR, TSLP protein receptor (also known as CRLF2).

Table 1 |

Summary of studies linking food sensitivity and microbial factors

Food sensitivity	Outcome	Study type	Refs
Coeliac disease	Intestinal dysbiosis in coeliac disease	Humans (children and adults)	54-57,59,67
	Altered duodenal microbiota in treated coeliac disease non-responding to gluten-free diet	Humans (adults)	58
	Association with environmental practices altering intestinal microbiota (caesarean section and antibiotic and PPI intake) and coeliac disease	Humans (children and adults)	36,37
	Severity of gluten immunopathology in mice is dependent on gut microbiota background	Mouse models	68
	Implication of gut microbiota in gluten metabolism and gluten-peptide immunogenic modification	In vitro and mouse models	6,85
Food allergy	Association of infections with coeliac disease and incitement of food sensitivity by virus	Humans (adults) and mouse models	5,41-44,46,52
	Inflammatory responses to microbial ligands in cells of carriers of the coeliac disease-associated risk allele <i>SH2B3</i>	In vitro and humans (adults)	177
	Association of bacterial richness in early infancy and food allergy	Humans (children)	60,61
	Association of specific bacterial profiles with food allergies	Humans (children and adults)	62,65,66
	Enteric infection can act as an adjuvant for the response to dietary antigens in food allergy	Mouse models	48
	Commensal bacteria regulate the production of IgE and increase susceptibility to food allergy in animal models	Mouse models	69,70
	Commensal bacteria protect against food allergy in animal models	Mouse models	71-73
	Association of single nucleotide polymorphisms in microbial sensing receptors and atopy	Humans (children and adults)	151-153

PPI, proton-pump-inhibitors; IgE, immunoglobulin E.