Adverse reactions to food, expressed as food sensitivity or food intolerance, are on the rise. This increase in prevalence cannot be explained by genetic drift, suggesting a critical role of yet unknown environmental factors as modifiers of disease expression. 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. However, the specific mechanisms behind these associations remain unclear. In this Review, we examine two 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 antigenicity or in the production of metabolites that directly affect tolerogenic responses. We also discuss treatment strategies designed to target these pathways that could be developed to prevent or better treat food sensitivities.

Food sensitivities with allergic pathophysiology involve immunoglobulin E (IgE) mechanisms, non-IgE-mediated mechanisms or a combination of both. IgE-mediated food allergy requires sensitization characterized by production of food allergen-specific IgE. Upon re-exposure to the allergen, allergen-specific IgE, which is bound to FcεRI (also known as FCER1A) on mast cells and basophils, becomes crosslinked and
**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 naïve 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.

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As with other food sensitivities and autoimmune diseases, the prevalence of coeliac disease is increasing worldwide. 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.

### 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. 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. 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, suggesting that repeated microbial infections early in life trigger food sensitivities, particularly in individuals with more moderate genetic predisposition. 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).

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<table>
<thead>
<tr>
<th>Conditions</th>
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<td>Autoimmunity</td>
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In addition to the support provided by clinical and epidemiological studies for an association between intestinal bacterial and viral infections and food sensitivities, the role of a dysbiotic gut microbiota has also been evoked. Indeed, several groups have reported intestinal dysbiosis in coeliac disease and food allergy. 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 mediation. In addition, coeliac disease-associated dysbiosis seems to be characterized by Proteobacteria expansion and the presence of opportunistic pathogens in the proximal small intestine. 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. 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 enterotypes. Others indicated that short-term diet alters microbial community structure, gene expression and metabolite production. 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. 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) butyrate (Fig. 2). In addition, the gut microbiota has the capacity to modify the chemical structures of numerous dietary molecules, including allergens or antigens.

**Immunogenicity of food antigens.** The intestinal microbiota is considered a metabolic organ that vastly complements the host’s metabolic activities. 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 inflammation. Gluten is a mix of proteins rich in proline and glutamine residues that confer unusual resistance to degradation by mammalian enzymes. 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 disease. 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. Caminero et al. 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 peptides (Fig. 2). For instance, specific opportunistic pathogens such as *Pseudomonas aeruginosa* further degrade digestive protease-modified gluten peptides.

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*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. AT1, α-amylase–trypsin inhibitor; IgE, immunoglobulin E.
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 pathogenic proteases. 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 intestine, have been reported to be more abundant and diverse in healthy individuals than in patients with coeliac disease. Further studies are required to test whether this reduced abundance of lactobacilli 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 onset.

Modification of gluten by the intestinal microbiota is not limited to its degradation. Gluten deamination — 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 process. TGase2 converts gluten amides to glutamates, 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 gluten. 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 proteases. 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) 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.

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<td>Commensal bacteria regulate the production of IgE and increase susceptibility to food allergy in animal models</td>
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PPI, proton-pump inhibitors; IgE, immunoglobulin E.
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 function. Many of these effects are mediated by immunomodulatory metabolites that result from the bacterial metabolism of dietary substrates. Products of bacterial metabolic activity, such as 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. 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. A non-balanced diet can promote a microbiota with a lower diversity and metabolic output. The lack of bacterial metabolites may result from dietary patterns or deficiencies of certain minerals. A high-fibre diet can reshape 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 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. 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 IFNγ). 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.
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 permeability\(^7\). In addition, IL-15, a pro-inflammatory cytokine upregulated in the epithelium and the lamina propria in coeliac disease\(^8\), 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 inflammation\(^9\). 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 gluten\(^10\). 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 microbiota\(^11\). 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 cells\(^12\).

Another emerging example relates to the production of aryl hydrocarbon receptor (AhR) ligands by microbial metabolism of dietary substrates rich in tryptophan\(^13\). 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\(^14,15\). 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\(^11,16,17\). Activation of AhR positively affects DC phenotype and function during allergic sensitization and could lead to protection in a mouse peanut allergy model\(^18,19\). 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 production\(^10\) and pT\(_{reg}\) cell differentiation\(^11,12,13\). Accordingly, germ-free mice have been shown to develop more severe allergies\(^14\) and more severe immunopathology in mouse models of gluten sensitivity\(^15\). 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\(^16,17\). The use of certain live bacteria as a probiotic treatment with either mouse-derived or human-derived strains attenuated food sensitivity\(^18,19,20,21\). 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 diseases\(^22\), which is in line with evidence that signals from the commensal microbiota suppress IgE production and basophil development\(^13\). 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\(^23,24\). 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 components\(^25\). 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 mice\(^26\). Interestingly, serpin expression has been identified to be specifically reduced in the small intestine of patients with coeliac disease\(^27\). Furthermore, extracellular vesicle-derived protein from B. longum KACC91563 was shown to alleviate food allergy through mast cell suppression\(^28,29\). 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 age\(^30\). The use of dead bacteria such as Escherichia coli for encapsulation of modified peanut protein has also been proposed\(^31\).

**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\(^32,33\). 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 signaling 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. In addition, coeliac disease is characterized by a leaky intestinal barrier, and an increased intestinal permeability is suspected to trigger the sensitization towards dietary antigens in food allergy. Most importantly, it is suspected that frequent microbial infections involving the intestinal tract could increase intestinal permeability. 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. Pathogens might alter the intestinal mucous layer by either improving mucus degradation or inhibiting the normal commensal cues for mucus production. Moreover, the intestinal epithelium influences tolerance to microbial or food antigens and/or allergens by conditioning mucosal APCs towards either development of CD103+ tolerogenic DCs, by releasing transforming growth factor-β (TGFβ) and RA, or under homeostatic conditions, or a pro-inflammatory T helper 1 (Th1) cell or Th2 cell response when barrier function is disrupted.

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 sensitivities. Furthermore, it has been suggested that dietary antigens can also be recognized by PRRs. In this context, the previously mentioned wheat proteins, ATIs, could have an important role, particularly for coeliac disease and NCWS. On the other hand, TLRs, such as TLR4, are thought to be essential for the maintenance of intestinal homeostasis. For instance, TLR4-dependent signals provided by the microbiota inhibit the development of allergic responses to food allergens according to experimental evidence. There is also an association of food sensitivities with single nucleotide polymorphisms in microbial sensing receptors such as TLR6 or TLR9 (REFS). This finding is in accordance with a study showing that enteric type 1 strain Lang (T1L) reovirus infection induces pro-inflammatory IL-12 production by mucosal Leishmania major and RA-dependent mechanism. Esterházy et al. demonstrated that the mucosal interferon regulatory factor 8 (IRF8)-dependent CD103+CD11b+ DC subset contains the most potent inducers of pTreg 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 dehydrogenase. The maturation and maintenance of this highly tolerogenic CD103+ DC subset are dependent on enteric environmental conditions, and an alteration of RALDH2 activity is associated with impaired oral tolerance in animal models. However, it is intriguing that the DC subset with the greatest tolerogenic potential also expresses pro-inflammatory IL-12 and IL-15 and drives Th1 cell responses to intestinal infections. This DC subset also expresses Tlr9, which binds bacterial and viral DNA, and triggers signalling cascades that lead to a pro-inflammatory cytokine response.

Intestinal inflammation abrogates the ability of CD103+ DCs to promote pTreg cell differentiation, 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 Th1 cell immunity in mice. Similarly, fungal infection with Encephalitozoon cuniculi induced a pro-inflammatory programme in lamina propria-residing, IL-12-producing CD103+CD11b+ CD8+ DCs in mice. This finding is in accordance with a study showing that enteric type 1 strain Lang (T1L) reovirus infection induced pro-inflammatory IL-12 production by mucosal CD103+CD11b+ DCs, which drove Th1 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 Th1 cell responses to dietary antigens, it is not required for blocking the pTreg cell induction that requires type 1 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 1 interferon or virus-mediated upregulation and release of the enzyme tissue transglutaminase. In a 2017 study, these associations were moved towards causality, and as a consequence of virus–host interactions, the pTreg cell response was abrogated, and a pathogenic Th1 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 pTreg cell induction through type I interferon-mediated pathways. By contrast, T1L cell induction in response to oral antigen was independent of type I interferon but required the transcription

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 (S IgA) 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 produce retinoic acid (RA) and that migrate to the mesenteric lymph nodes to promote the differentiation of naïve CD4+ T cells into peripherally derived forkhead box protein P3 (FOXP3)− regulatory T (Treg) cells (pTreg cells) via a transforming growth factor-β (TGFβ)− dependent and RA− dependent mechanism. In the lamina propria, tolerogenic pTreg 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 (Th1) cell response to gluten that leads to IEC destruction and villous atrophy. T1L 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 Th1 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 pTreg cells. Food allergy is mediated by Th2 cell responses to dietary antigens. Microbial infections inducing IL-4, IL-5 and IL-13 could also contribute to promoting Treg 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).
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 titres, 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 pTreg cell response and instead driving a Treg cell response that leads to LOT and food antigens and whether this process could have important implications in other food sensitivities.

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 LOT106,173 and to be upregulated upon stimulation with lipopolysaccharide or double-stranded RNA174. Interestingly, IL-15 is not implicated in reovirus-mediated LOT1, 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 pTreg cell differentiation and induces Treg cell responses to dietary antigens106,173. These findings are relevant to coeliac disease173, in which polymorphisms in the gene encoding IL-12 are suggested to be a genetic risk factor and in which IL-15 upregulation in the lamina propria is associated with an upregulation of IL-12 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 Treg cell immunity181,182 (FIG. 3). A population of small intestinal CD103+CD11b+ DCs were shown to mediate mucosal Treg cell responses against parasites in mice, and it was also shown that IRF4 is involved and dependent on the type of microbial trigger. 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 Treg2 cell responses184,185; however, precise mechanisms are lacking. In general, the helminth-elicited Treg 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 function187. 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 mice188. Future studies are required to clearly define the microbial-triggered Treg 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 Treg 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 microorganism–diet interactions and their underlying molecular pathways will be necessary to develop prevention and novel therapies to treat food sensitivities.

Published online: 13 September 2018

Box 1 | 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.


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 antigens.


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 antigens into the systemic circulation and contributing to protection against food sensitization.


84. 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.


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).


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. colonisation promotes sensitization against food antigens, at least partly owing to mast cell-mediated hyperpermeability in the gastrointestinal mucosa of mice.