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The role of gastrointestinal permeability in food allergy

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Key Messages

- Selective intestinal epithelial permeability is essential for uptake of water and nutrients and contributes to oral tolerance development.
- Altered intestinal epithelial barrier function and composition is observed in food allergy.
- Subepithelial mediators and small intestinal luminal content influence barrier integrity.
- The gastric milieu and physiological function contribute to antigen separation from the immune induction sites.
- A dysfunctional barrier of the entire gastrointestinal tract has an essential contribution to food allergic reactions.

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Introduction

The human gastrointestinal tract is composed of several organs with a complex cellular and functional structure. The intestinal tract not only is responsible for the breakdown and absorption of essential nutrients and the uptake of electrolytes and water, but also represents a crucial component of the body's defense system against the external environment.[1] With its barrier, the intestinal tissue contributes to the first defense line in the human body composed of a static epithelial and dynamic luminal and subepithelial layer. Even though being found inside the body, the intestinal epithelium is the largest surface to the outside environment and consists of a single layer of cells composed of diverse cell types covering an enormous surface area. The epithelial surface is organized into crypts, villi, and folded in countless plicae and microvilli continually being renewed by pluripotent intestinal epithelial stem cells residing at the base of the crypt-villus axis. Intestinal epithelial stem cells mature to various subtypes of intestinal epithelial cells (IECs). Four essential cell types of the epithelial layer have been defined.[1] Besides absorptive enterocytes and mucus-secreting goblet cells,[1] Paneth cells are specialized for maintaining the bacterial gradient along the crypt-villus axis by secretion of antimicrobial products such as lysozyme, α-defensins, or cryptdins.[2] Additionally, enteroendocrine cells connect the central nervous system with the enteric neuroendocrine system by secretion of hormones regulating digestive functions.[1] On differentiation of intestinal epithelial stem cells to enterocytes, the intercellular seals of the epithelial layer such as tight junctions (TJs) and adherent junctions are formed.[1]

Because of the high number of immune cells residing underneath IECs, the small intestine is considered the main organ in oral tolerance development and also in food allergy induction.[3] Therefore, the previously mentioned cells and structures play an important role not only by influencing epithelial permeability, allowing immunologically active dietary compounds to get in contact with mucosal immune cells, but also by orchestrating the immune response associated with food-specific reactions. In this review, we specifically aim to highlight the role of the gastrointestinal barrier function in food allergy.

Composition of the Intestinal Epithelial Barrier in Health

The static epithelial barrier is composed by IECs interacting with each other via a complex multilayer system. On the apical intercellular space of IEC, TJ proteins form complex paracellular barriers

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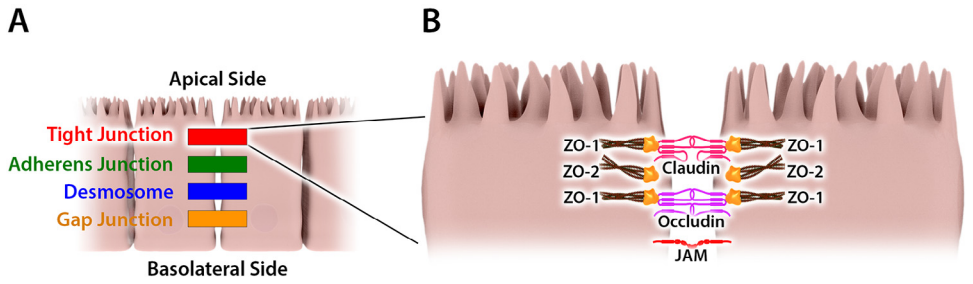

Figure 1. Composition of the paracellular multiprotein complex essential for formation of a tight epithelial barrier by adjacent intestinal epithelial cells. Together with adherent junctions, desmosomes, and gap junctions, tight junctions found on the apical part of intestinal epithelial cells limit the paracellular passage of ions, electrolytes, and macromolecule (A). Tight junctions are composed of integral proteins such as claudin (red) and occludins (purple), which are attached to the cytosolic scaffold proteins' zonula occludens. Zonula occludens proteins (ZO-1, ZO-2) anchor tight junction proteins to the actin cytoskeleton. The junctional adhesion molecules (JAM) furthermore regulate tight junction protein interactions (B).

and pores regulating the paracellular passage of ions and molecules.[4] Further toward the basolateral side of the IECs, the paracellular transport is limited by adherent junctions, desmosomes, and gap junctions (Fig 1A).[4]

The epithelial TJ is a multi-protein complex that forms a selectively permeable seal between adjacent epithelial cells and creates the boundary between apical and basolateral membrane domains.[4] The TJs maintain the intestinal barrier while regulating permeability of ions, nutrients, and water.[5] Four integral transmembrane proteins, occludin, claudins, junctional adhesion molecule (JAM), and tricellulin, have been characterized and the intracellular domains of these transmembrane proteins are linked to cytosolic scaffold proteins, such as zonula occludens (ZO) proteins. The ZO proteins interact with the actin cytoskeleton, being crucial for maintaining the TJs' structure and for modulating barrier integrity (Fig 1B).[5]

The dynamic part of the intestinal barrier is composed of the luminal microbiota and mucus as well as epithelial and immune cell products secreted into the lumen (Fig 2). The intestinal microbiota is involved in metabolic, nutritional, and immunological processes in the human body. By extracting energy from indigestible dietary polysaccharides such as resistant starch and dietary fibers, gut commensals exert essential metabolic activities. Furthermore, the intestinal microbiota participates in the defense against harmful pathogens by different mechanisms such as colonization resistance and production of antimicrobial compounds. Additionally, the intestinal microbiota is involved in the development, maturation, and maintenance of the gastrointestinal sensory and motoric functions.[6]

Of interest, IECs act as frontline sensors for epithelial contact with microbes and are able to convert bacteria-derived signals into antimicrobial and immune-regulatory responses. The IECs express pattern-recognition receptors for direct interaction with the microbial environment, enabling them to participate in a specific mucosal immune response. The expression of toll-like receptors,

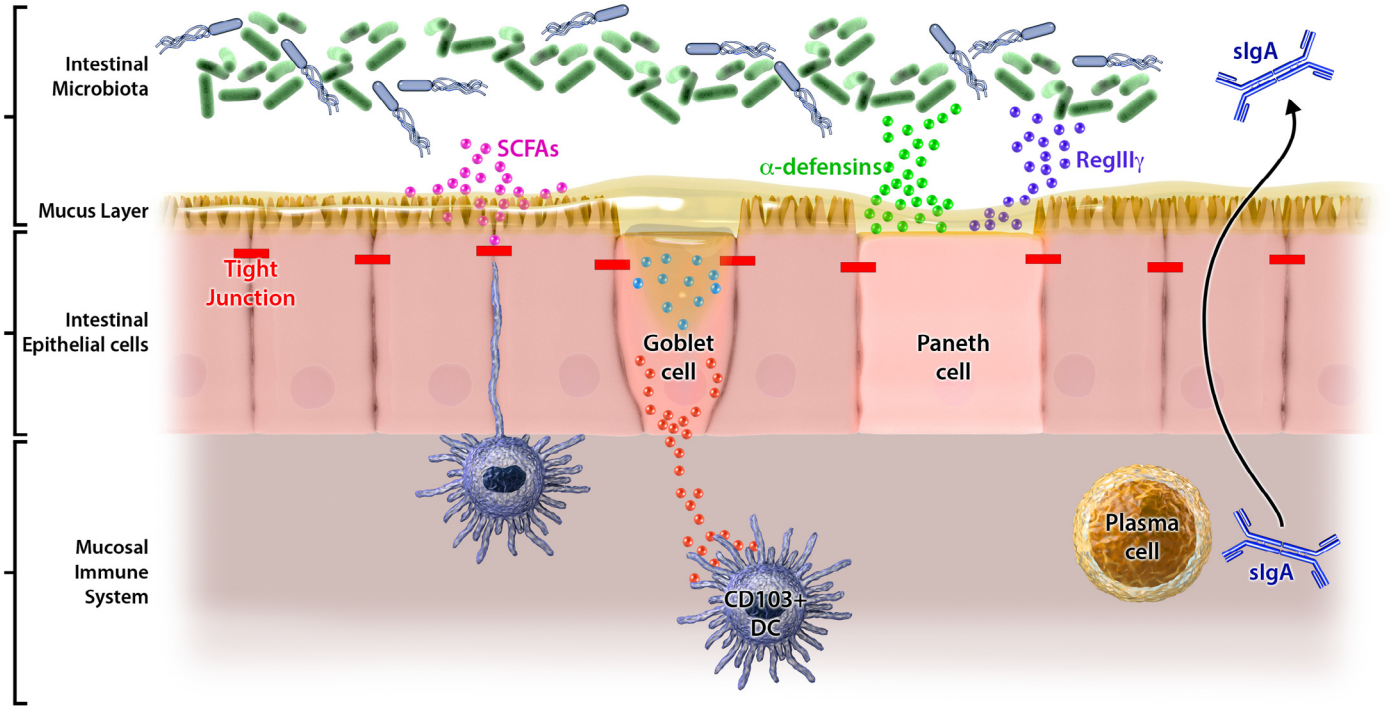

Figure 2. Structure of the intestinal barrier. The multiple layers of the intestinal epithelial barrier are responsible for spatial segregation of antigens and pathogens from intestinal epithelial cells and immune induction sites. On the luminal side, commensal bacteria, antimicrobial products such as α-defensins, and secretory immunoglobulin A antibodies as well as the mucus layer limit interaction of pathogens with epithelial cells. Under healthy conditions, intestinal epithelial cells form a tight monolayer, allowing only selective permeability. Below the epithelial layer, the mucosal immune system contributes to the epithelial barrier function.

nucleotide-binding oligomerization domain (NOD)-like receptors and retinoic acid-inducible gene-1(RIG-I)-like receptors on and in IECs provide distinct pathways for recognition of microbial ligands or endogenous signals associated with pathogenesis.[7–9] Additionally, the abundance of signals from commensal bacteria in the intestine induces a state of altered responsiveness in IECs.[1]

The intestinal epithelium is furthermore covered by a thick mucus layer with large mucin glycoproteins as the major component. Secreted by goblet cells, the mucus provides an important physical and biochemical barrier to prevent microbial contact with epithelial surface by entrapping noxious molecules as well as pathogens (Fig 2).[10]

For maintenance of the intestinal homeostasis, secreted antimicrobial products such as α-defensins, lysozyme C, and RegIIIα (or RegIIIγ in mice) released by Paneth cells, as well as immunoglobulin (Ig) A produced by plasma cells prevent pathogens' adhesion and colonization.[2,11] All of these antimicrobial products are essential for the spatial segregation of luminal commensals and pathogens from the intestinal epithelium. Whereas α-defensins act against both gram-positive and gram-negative bacteria, the lectin RegIIIγ specifically targets gram-positive bacteria by binding to their surface peptidoglycan layer.[11] Immunoglobulin A, dimeric in the secretory form (sIgA), is the most abundant mucosal immunoglobulin isotype. Produced by specialized plasma cells found in the lamina propria, sIgA binds to specific Fc-receptors on the basolateral side of the IECs responsible for transcellular shuttling into the intestinal lumen (Fig 2).[2]

Underneath the epithelial layer in the lamina propria, most scattered intestinal immune cells and tissue-specific organized lymphoid structures, such as Peyer's patches, found below specialized micofold (M-) cells, cryptopatches, and isolated lymphoid follicles, are located. The intestinal immune system is additionally composed by intraepithelial effector lymphocytes interspersed in the epithelial lining and by extraintestinal outposts such as the mesenteric lymph nodes. Not only effector T and B lymphocytes provide the host with potent, adaptive immune responses. An effective immune response depends to a great extent on innate immune cells such as dendritic cells, monocytes/macrophages, and the heterogeneous group of innate lymphoid cells in the intestine.[12]

Intestinal Barrier Homeostasis and Barrier Dysfunction

To ensure adequate uptake of water and nutrients, a selective intestinal permeability is essential. The paracellular uptake of water, ions, and bigger molecules is limited by TJs as a size and charge selective flux is regulated by claudin proteins.[13] Additionally, antigen uptake might take place through the epithelial layer. One pathway is shuttling of soluble and aggregated antigens or immune complexes through M-cells, which are also termed port to the gut associated lymphoid tissue.[14] Conversely, antigens are taken up through the transcellular route, which is associated with lysosomal antigen degradation. This selective and balanced permeability is essential not only for adequate nutrition but also for oral tolerance development.[15]

However, a number of intestinal and extra-intestinal diseases are described as being associated with a changed intestinal barrier function and increased permeability. Among them, irritable bowel syndrome, inflammatory bowel disease, celiac disease, and extra-intestinal diseases such as type 1 diabetes as well as colorectal cancer and acute inflammation–like sepsis were described to be associated with a leaky gut.[16,17] For these diseases, an impaired barrier was even found to precede disease onset, and also changed TJ compositions were described in the scientific literature.[16]

As mentioned, the selective permeability of the intestinal barrier is essential for oral tolerance development. Therefore, speculating that the breakdown of oral tolerance to food, that is, food allergy, is associated with a changed intestinal barrier function is tempting.

Intestinal Epithelial Barrier Dysfunction: A Risk Factor for Food Allergy?

Oral tolerance is the key mechanism to guarantee human health[15] by ensuring the absence of adverse immune responses to harmless food proteins that are essential to nourish the human body. Tolerance mechanisms are furthermore of importance to distinguish innocuous commensals from harmful pathogens in the intestine.[18] Food allergies are defined as reproducible, adverse immune responses toward dietary compounds associated with detrimental health effects.[19] As diagnosed by food challenges, up to 10% of the population is affected by food allergies, with increasing prevalence over the past decades.[19] A large variety of risk factors have been described to be associated with the development of food allergies, such as genetics, epigenetic effects, and environmental stimuli, but also nutritional aspects such as fat and antioxidants consumption, as well as route of food allergen exposure.[19,20]

Impaired skin barrier because of inflammatory processes or genetic mutations was found to be associated with food allergy development caused by cutaneous exposure to proteins causative for sensitization.[21,22] In addition, the intact intestinal epithelial barrier seems to play an important role in food allergies. In experimental animal models as well as clinical studies, food allergy was described as being associated with an apparent defect of the intestinal barrier function.[23–28]

In early studies, altered carbohydrate absorption patterns were reported in food-allergic patients after allergen challenge compared with healthy controls and with allergic patients under allergen exclusion diets.[23,25] This is in contrast to pollen-allergic children with rhinoconjunctivitis showing no changes in the intestinal permeability during and after 3 months' oral immunotherapy with encapsulated birch pollen preparations.[29] In food allergies, a significant correlation between increased permeability as defined by changed urinary lactulose-to-mannitol ratio and symptom severity was observed.[27] The enhanced permeability was even noted in food-allergic children on a specific elimination diet showing limited growth.[26] In an experimental animal model, an enhanced systemic allergen uptake on oral challenge was detected to be associated with food allergy after oral sensitization under concomitant gastric acid suppression.[24]

The enhanced permeability toward food compounds as observed in ongoing food-allergic reactions might be attributable to different mechanisms in a sensitized intestinal epithelium. An IgE-CD23–mediated, bidirectional transcellular allergen transport was described in food allergy as being able to deliver allergens immunologically intact across the intestinal epithelium.[30] Moreover, for mast cell activation and release of proteases and inflammatory cytokines, a direct influence on TJ architecture by TJ protein rearrangement has been described. The mast cell granula content chymase was demonstrated to increase paracellular permeability, associated with uptake of intact antigens through the disrupted intestinal barrier in an experimental murine model.[31] Furthermore, mast cell protease-1 degrades the TJ protein occludin, associated with increased epithelial permeability during nematode infections.[32] Although under physiological conditions occludin is concentrated at the TJs, tumor necrosis factor alpha secretion is associated with an increased myosin light chain kinase activity, which induces occludin endocytosis, leading to enhanced paracellular permeability.[33] In line, treatment with tumor necrosis factor alpha–specific antibody was shown to correct the dysfunctional intestinal barrier in patients with Crohn's disease.[34] Being associated with reduced epithelial barrier integrity, interleukin-13 was shown to trigger claudin-2 expression by surface epithelial cells in the inflamed gut, which do

Table 1
Influence of Various Factors on Intestinal Barrier Integrity

Factors influencing intestinal permeability	Target proteins or readout	Model system	Ref.
Purified dietary components or food extracts, eg, gliadin and spices (such as cayenne pepper and paprika)	TJ protein modulation, cytoskeleton rearrangement, epithelial barrier integrity (TEER)	Intestinal epithelial cell lines	37
Food allergens, eg, Act d1, β-lactoglobulin	TJ protein modulation, epithelial barrier integrity (TEER)	Mouse model	38
Sphingosine-1-phosphate (S1P)	Epithelial barrier integrity (TEER), transepithelial allergen uptake	Intestinal epithelial cell lines, mouse model	39
High-fat and high-sugar Western diet, with or without fructose	Transepithelial antigen (LPS or HRP) uptake, mucus thickness, and microbiota composition	Mouse and rat model	41,42
Probiotic treatment, eg, *Escherichia coli* Nossle, *Bifidobacterium infantis* Y1, and *Lactobacillus plantarum*	TJ protein modulation, epithelial barrier integrity (TEER)	Intestinal epithelial cell lines, mouse model	37
Microbial products, eg, cholera toxin and staphylococcal enterotoxin B	TJ protein modulation, transepithelial antigen (HRP) uptake	Mouse and human intestinal tissue	36
Microbial changes associated with limited dietary fiber intake	Carbohydrate active enzyme expression	Mouse model	43

Abbreviations: HRP, horseradish peroxidase; LPS, lipopolysaccharide; TEER, transepithelial electrical resistance.

not express this TJ protein under physiological conditions.[33,35] In duodenal biopsies of patients with food allergy, higher expression levels of the pore-forming TJ protein claudin-2 were found compared with patients with duodenal peptic ulcers.[36]

Small Intestinal Luminal Content Influences Barrier Integrity

Not only inflammatory mediators being released on the basolateral side of the epithelium directly affect epithelial TJ architecture and protein expression. The luminal content substantially impacts on the intestinal epithelial barrier function, with the limitation that more clinical studies are required to confirm the relevance for human patients. In vitro studies using intestinal epithelial cell lines revealed effects of numerous dietary components such as gliadin, spices, and herbs on TJ protein rearrangement, paracellular ion flux, and overall epithelial barrier integrity.[37] The known kiwifruit allergen Act d1, which has a cysteine protease activity, was shown to disrupt the TJ protein network and to impair epithelial barrier integrity.[38] Moreover, fat content of the human diet influences the epithelial integrity. Incubation of IECs in a transwell model with the bioactive lipid mediator sphingosine-1-phosphate was associated with decreased barrier integrity and enhanced allergen uptake in a time-dependent manner with impact on food allergy induction in an experimental animal model.[39] Although supplementation of polyunsaturated fatty acids was reported to be associated with protection and repair of intestinal barrier in inflammation,[40] 2 recent studies in mouse models demonstrated a clear correlation between ingestion of Western diet characterized by high fat and high sugar content and an increased transepithelial antigen uptake, reduced mucus thickness, and changed microbiota composition.[41,42] Additionally, the microbiota composition might substantially influence epithelial barrier function. Commensals and probiotic bacteria such as *Escherichia coli* Nissle 1917, *Bifidobacterium infantis* Y1, and *Lactobacillus plantarum* were demonstrated to enhance barrier integrity by a changed TJ protein composition and up-regulation of ZO-1, ZO-2 and occludin expression.[37] Conversely, detrimental microbial products such as Cholera toxin and Staphylococcal enterotoxin B were reported to be associated with increased claudin-2 expression and enhanced transepithelial antigen transport in mouse intestinal tissue.[36] Of interest, these bacterial products are frequently applied for oral immunizations together with food proteins to induce food allergy in experimental animal models. Moreover, microbial changes associated with limited dietary fiber intake might result in degradation of the gut mucus glycoproteins by the microbiota, resulting in mucus erosions and susceptibility to inflammations[43] (Table 1).

In the intestinal tract, mucus seems to have a more sophisticated role than a simple nonspecific physical barrier function. In experimental mouse models, luminal antigens were shown to be delivered together with MUC2 proteins to subepithelial tolerogenic dendritic cells via shuttling through goblet cells with major impact on oral tolerance development.[44] In line, MUC2-deficient mice had a higher number of IEC-adherent microbes and did not develop antigen-specific tolerance to orally administered dietary proteins.[44] Despite all of these mechanistic studies, whether increased intestinal permeability being associated with TJ protein rearrangements, mucus, or microbiota changes is cause or consequence in food allergy remains unclear. Even though a clear association exists of intestinal barrier dysfunction with inflammatory bowel disease,[16] the impact of the intestinal epithelial integrity on food-adverse reaction is less evident. Disruption of the intestinal barrier might not be the only decisive factor for food allergy induction. Early studies demonstrated an enhanced antigen uptake through the gastric mucosa on *Helicobacter pylori* infections, and these infections were also reported to correlate with food allergy development in children.[45,46] Thus, not only a dysfunctional intestinal barrier but an impaired barrier of the entire gastrointestinal tract might contribute to food allergies.

The Influence of the Gastrointestinal Barrier on Food Allergy

As outlined, the epithelial barrier plays a major role in the immune homeostasis of intestinal tract by separation of antigens, pathogens, or commensals from the epithelial layer to prevent interaction of intact antigens or bacteria with the epithelial layer.[47] Nevertheless, the physiological function of the entire gastrointestinal tract contributes to antigen degradation and prevents pathogen colonization. Thus, the denaturing activity of gastric acidity, protein degradation by gastric, pancreatic, and small intestinal brush-border enzymes, and the size-dependent filter properties of the intact mucus layer contribute to antigen and pathogen segregation from the epithelial layer. That the acidic milieu of the stomach prevents intestinal pathogen colonization is increasingly recognized.[48] Hypoacidity of the stomach induced by the use of proton pump inhibitors is associated with changed composition of the intestinal microbiota and a significant increase in the relative abundance of specific bacterial stains.[49,50] This effect could be attributed either to direct targeting of bacterial or fungal H + /K+-adenosine triphosphatases or indirectly to the microenvironment via pH changes.[51] A recent meta-analysis revealed proton pump inhibitors to have a more prominent effect on microbiota composition on a population basis than antibiotics or any other drugs.[52] Additionally, a functional gastric protein digestion degrades potent food allergens, resulting in a reduced biological activity and allergenicity of dietary antigens, whereas hypoacidity of simulated gastric fluids was associated with impaired protein digestion.[53,54] In line with these results, experimental animal as well as human clinical studies demonstrated the impact of gastric acid suppression in food allergy. In

experimental mouse models, oral gavage of digestion-labile food allergens together with anti-acids or anti-ulcer medication or even base powder resulted in formation of allergen-specific IgE antibodies, positive skin tests, drop of core body temperature, and an enhanced mast cell mediator release, which are both associated with anaphylactic reactions.[24,39,55–58] Moreover, an influx of inflammatory cells into the gastric and intestinal mucosa and a changed mucosal architecture was detected after food allergy induction in mice.[58,59] In human patients being treated with anti-ulcer medication because of dyspeptic disorders, a boost or de novo IgE formation toward regular constituents of the daily diet was detect after 3 months of medication intake.[60] Development of hazelnut allergy could be diagnosed by double-blind placebo-controlled food challenges in adult patients after gastric acid suppression.[57] Also, for pediatric patients, an impact of drug-induced gastric acid suppression on food allergy development was reported.[61,62] Even during pregnancy, maternal anti-ulcer drug intake was found to be associated with a higher risk for childhood allergy development.[63–65] Additionally, in patients with diagnosed food allergies, a functional gastric protein digestion is of relevance. A clinical study indicated significantly changed clinical reactivity toward fish proteins digested by gastric enzymes compared with allergens that remained undigested.[66] Thus, the physiological gastric barrier seems to play an essential role in food allergy, and a clear correlation of an impaired gastric gate-keeping function and food allergy induction and food adverse reactions was repeatedly reported.[53]

Conclusion

The reviewed studies combine information from different fields of clinical and experimental research, with the aim to highlight current knowledge on the influence of barrier function in food allergy. Undoubtedly, the question of whether barrier dysfunction influences food adverse reactions can only be answered by an integrated approach. Despite numerous mechanistic studies indicating a paramount influence of the different layers of the intestinal barrier on oral tolerance development or tolerance breakdown (Table 2), the different compartments of the entire gastrointestinal tract contribute to the separation of dietary or microbial antigens from immune induction sites in the gastrointestinal tract. Thus, a constant interaction of the gastrointestinal barrier, the host physiology, and the gastrointestinal luminal content, such as digestion and uptake of food compounds and antigen exclusion or selective permeability, occurs, which in concert ensure an appropriate immune response and overall health (Fig 3). Certainly, further studies are needed to define whether enhanced permeability is cause or consequence of food allergy and to evaluate the interaction of different layers of the gastrointestinal barrier. Undoubtedly, other factors, such as, for example, the route of primary allergen exposure and the genetic background, contribute to food allergy development.

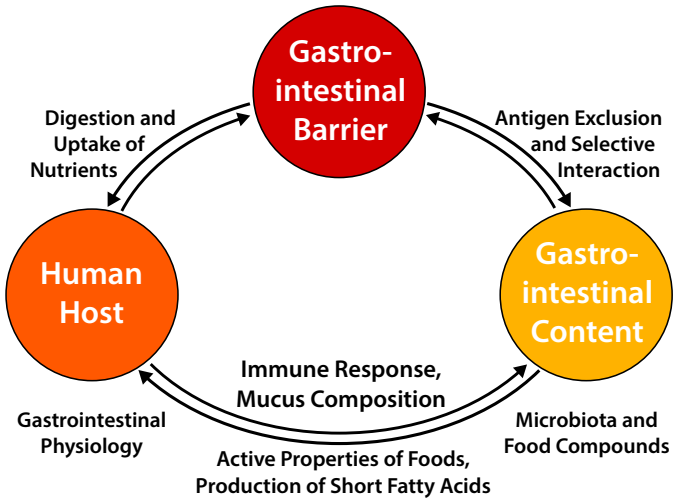

Figure 3. Interplay of the gastrointestinal barrier with the luminal content and the host physiology in food allergy. The different layers of a functional gastrointestinal barrier as well as the gastrointestinal physiology are in close interaction with the luminal food and microbiota content to prevent the development of food-adverse reactions.

Nevertheless, that the functional integrity of the gastrointestinal barrier plays an important role in prevention of IgE-mediated reactions toward dietary compounds can be clearly stated.

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Table 2
Physiological Features of Gastrointestinal Compartments Contributing to the Separation of Food Protein Antigens From Immune Induction Sites

Location	Active layer	Functionality
Gastric environment	Acidic luminal gastric milieu	Protein denaturation
	Gastric enzymes	Reduction of antigen load by protein digestion
	Gastric mucus	Segregation of antigens from epithelium
	Epithelial layer	Tight barrier toward the external environment limiting antigen uptake
Intestinal environment	Commensal microbiota	Metabolism of nutrients; cross-talk with immune system and delivery of tolerogenic stimuli
	Mucus layer	Physical barrier, contribution to oral tolerance
	Pancreatic and small intestinal brush-border enzymes	Reduction of antigen load by protein digestion
	Secretory products of IECs	Immune-stimulating activity
	Epithelial layer	Selective and balanced barrier for uptake of nutrients and oral tolerance development

Abbreviation: IECs, intestinal epithelial cells.

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