Invited Review Article

A comprehensive understanding of the gut mucosal immune system in allergic inflammation

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Abstract

Despite its direct exposure to huge amounts of microorganisms and foreign and dietary antigens, the gut mucosa maintains intestinal homeostasis by utilizing the mucosal immune system. The gut mucosal immune system protects the host from the invasion of infectious pathogens and eliminates harmful non-self antigens, but it allows the cohabitation of commensal bacteria in the gut and the entry of dietary non-self antigens into the body via the mucosal surface. These physiological and immunological activities are regulated by the ingenious gut mucosal immune network, comprising such features as gut-associated lymphoid tissue, mucosal immune cells, cytokines, chemokines, antimicrobial peptides, secretory IgA, and commensal bacteria. The gut mucosal immune network keeps a fine tuned balance between active immunity (against pathogens and harmful non-self antigens) and immune tolerance (to commensal microbiota and dietary antigens), thus maintaining intestinal healthy homeostasis. Disruption of gut homeostasis results in persistent or severe gastrointestinal infection, inflammatory bowel disease, or allergic inflammation. In this review, we comprehensively introduce current knowledge of the gut mucosal immune system, focusing on its interaction with allergic inflammation.

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Introduction

The gastrointestinal tract—the tube-like structure covered by mucosa from the oral cavity to the anus—is continuously and directly exposed to inputs from the external environment and entry of dietary antigens and pathogens. A major physiological function of the gastrointestinal tract is the digestion of food, absorption of nutrients and water, and elimination of unnecessary wasted products; the intestine is a major site of entry for many bacterial and viral pathogens and has a vast and diverse microbial community.1–3 Despite the complexity of the outer environment, intestinal homeostasis is ingeniously maintained under the control of the unique gut mucosal immune network, which is characterized by such features as gut-associated lymphoid tissues (GALT or Peyer’s patches; PP), secretory IgA (SIgA), antimicrobial peptides (e.g., defensins), mucosal immune cells (e.g., Th1, Th2, Th17, Treg cells), cytokines (e.g., IL-10), chemokines (e.g., CCR9), and commensal bacteria.3–5

Food allergy, which generally occurs in early childhood, is triggered by the ingestion of a dietary antigen via the gut mucosal membrane; it causes clinical signs such as gastrointestinal disorders, urticarial, and distant airway inflammation, ranging in severity from mild to life-threatening.5 Because the prevalence of food allergy seems to be increasing in developed countries,9,10 the development of the gut mucosal immune system is in influence by the outer environment in the form of nutrition and commensal bacteria.27–32 As an example of nutritional involvement, retinoic acid (RA), a metabolite of vitamin A, plays a crucial role in induction of the chemokine CXCL13 leading to the formation of lymphoid cell clusters (Fig. 1).24 Inhibition of RA synthesis reduces the formation of LTi cell-mediated lymphoid cell clusters; therefore, maternal levels of dietary retinoids control the size of secondary lymphoid organs in the gut.27 Commensal bacteria promote gut development. Compared with conventionally raised animals, germ-free animals have fewer goblet cells, a thinner mucus layer, reduced villus thickness, and impaired brush border differentiation.33 In addition, PPs and MLNs are underdeveloped in germ-free mice.34 In contrast, postnatal microbial colonization promotes the maturation of GALT including their size and the formation of germinal center in PPs.35 Bacterial products such as LPS and peptidoglycan have been shown to stimulate to establish conventional mucus properties as well as the maturation of GALT in germ-free mice.36,37

Development of the gut mucosal immune system

Food allergy tends to occur in early childhood (<2 years old), and immediate-type food allergy has the highest incidence in infants (<1 year old).9,10 Therefore, the interaction between this early food allergy and the development of the gut mucosal immune system is of particular interest. The gut mucosal immune system develops both anatomically and functionally with age dependent manner.8–20 Of the mucosa-associated lymphoid tissues (MALT), PPs and the mesenteric lymph nodes (MLNs), family of GALT begin developing during the fetal life, whereas isolated lymphoid follicles (ILFs) and nasopharyngeal-associated lymphoid tissue (NALT) develop and mature after the birth.14,15 In humans, aggregates of T lymphocytes that contain small numbers of B cells are the initial lymphoid structures (anlagen) of PPs and are seen in the fetus from 14 weeks of gestational age.10 The PPs increase in number and size with age until adolescence.18 In murine models, underdevelopment of MLNs or PPs, or both coincides the reduction of SIgA and oral tolerance and thus increases susceptibility to infection and food allergy.23–25 MLN- and PP-deficient mice show strong reductions in IgA-producing B-cell counts and increased susceptibility to Listeria monocytogenes infection.23 Oral tolerance fails to be induced in both MLN- and PP-deficient mice.24 In an ovalbumin (OVA)-induced allergy model, deficiency of PPs alone resulted in failed induction of oral tolerance to OVA and the development of severe allergic signs upon OVA challenge, unlike in wild-type mice.5,26 Moreover, the absence of MLNs alone is sufficient to impair the induction of oral tolerance to OVA.24 These findings suggested that the presence and maturation of GALT play one of key roles for the establishment of balanced gut mucosal immune system contrived by the SIgA and oral tolerance induction.

The cellular and molecular mechanisms of PP and MLN development have been clarified in murine studies. Although the development of PP and MLN structures is guided by different signals to some extent, in both cases development requires the interaction between lymphoid tissue inducer (LTI) cells (or currently termed as type 3 innate lymphoid cells: ILC3)27 and lymphoid tissue organizer cells (Fig. 1).15,26 In addition, the differentiation of LTI cells from IL-7Rá+ lymphoid progenitors requires the expression of inhibitor of DNA binding 2 (ID2) and the retinoic acid receptor-related orphan receptor γt (RORγt) in developing PPs and MLNs.29,30 Signaling via IL-7Rα and TNI receptor activates the cytokine receptor or both, leading to the differentiation of LTi1β2 by LTI cells, which promote lymphoid tissue formation.31 Development of the gut mucosal immune system is influenced by the outer environment in the form of nutrition and commensal bacteria.23–35 As an example of nutritional involvement, retinoic acid (RA), a metabolite of vitamin A, plays a crucial role in induction of the chemokine CXCL13 leading to the formation of lymphoid cell clusters (Fig. 1).24 Inhibition of RA synthesis reduces the formation of LTI cell-mediated lymphoid cell clusters; therefore, maternal levels of dietary retinoids control the size of secondary lymphoid organs in the gut.27 Commensal bacteria promote gut development. Compared with conventionally raised animals, germ-free animals have fewer goblet cells, a thinner mucus layer, reduced villus thickness, and impaired brush border differentiation.33 In addition, PPs and MLNs are underdeveloped in germ-free mice.34 In contrast, postnatal microbial colonization promotes the maturation of GALT including their size and the formation of germinal center in PPs.35 Bacterial products such as LPS and peptidoglycan have been shown to stimulate to establish conventional mucus properties as well as the maturation of GALT in germ-free mice.36,37

Gut mucosal barrier as the site of entry of dietary antigens and pathogens

Intestinal homeostasis is maintained largely by the harmonized physical, chemical and immunological defense system against pathogens (e.g., bacteria, viruses and fungi) and by immune tolerance to dietary antigens and commensal bacteria.38,39 In terms of the defense mechanism, mucosal surfaces in the small intestine are both specifically and non-specifically protected against pathogen invasion and unfavorable antigen entry into the body through both anatomical and immunologic defense mechanisms. As non-specific mechanisms, physical and chemical barrier comprising of intestinal epithelial cells covered with mucus layer and antimicrobial peptides (e.g., defensins and lysozymes) protects against pathogen invasion as a first line of defense.38 Intestinal epithelial cells, in association with fucose, the production of which is induced by commensal bacteria and ILC3, inhibit pathogenic bacterial infections (e.g., Salmonella typhimurium).30,40 Further, these fucosylation products are nutrients for some of commensal bacteria (e.g., Bacteroides and Lactobacillus).38 As an example of specific mechanisms, intestinal epithelial cells produce pro-inflammatory chemokines (e.g., MCP-1 and IL-8) and cytokines (e.g., IL-15) in response to luminal stimuli and induce the recruitment of diverse immune cells in the lamina propria (LP) to inflamed regions. In this...
Organizer cells. These adhesion molecules and chemokines promote the adhesion and attraction of LTi cells and the organizer cells, leading to the formation of the PP anlagen. In the development of MLNs, LTαβ12R expressed on the organizer cells, thus enhancing the close interaction between LTi cells and the organizer cells. This close interaction upregulates the expression of adhesion molecules (ICAM-1, VCAM-1, and mucosal vascular addressin cell adhesion molecule 1) that is capable of binding to LTαβ12R expressed on the organizer cells, thus enhancing the close interaction between LTi cells and the organizer cells. This close interaction upregulates the expression of adhesion molecules (ICAM-1, VCAM-1, and mucosal vascular addressin cell adhesion molecule 1) from the organizer cells, further recruiting LTi cells and enhancing the adhesion of migrated LTi cells and other immune cells (B and T cells and DCS). This is followed by the formation of the MLN anlagen. In the development of PPs and MLNs, RA induces the expression of CXCL13 by mesenchymal lymphoid organizer cells. CXCL13 then attracts LTi precursor cells from the blood to form the first lymphoid cell clusters. DC, dendritic cell; ICAM-1, intercellular adhesion molecule 1; LTi, lymphoid tissue inducer; MadCam-1, mucosal vascular addressin cell adhesion molecule 1; MLN, mesenteric lymph node; PP, Peyer’s patch; RA, retinoic acid; VCAM-1, vascular cell adhesion molecule 1.

regard, our recent study revealed that microRNAs, which are small noncoding RNA molecules such as miR-1224, miR-3473a, and miR-5128 that regulate transcription, are involved in homeostasis and disruption of the epithelial barrier via modulation of the expression of genes (e.g., AQP8 and ABCG2) in epithelial cells in the colon, rather than in the small intestine. Among these epithelial cells, goblet cells secrete mucins, which are major components of the mucus layer. Goblet cells also secrete other biologically active products contributing to innate immunity, such as trefoil peptides, resistin-like molecule β, and Fc-γ binding protein, which stabilize the mucus layer. Another type of epithelial cells, Paneth cells, located at the base of the intestinal glands, produce defensins, which kill or inactive bacteria by attacking their basic cell-wall structures. Lactofermin, a protein generally derived from breast milk, inhibits bacterial growth through iron-dependent and -independent mechanisms. Commensal bacteria indirectly affect the barrier functions of epithelial cells and help to inhibit allergic sensitization. Clostridial colonization induces IL-22 production by both RORγt+ ILCs and T cells in the LP and reduces the uptake of orally administered dietary antigens into the systemic circulation by the stabilization of intestinal epithelial permeability and thus contribute in the prevention of allergic diseases.

Secretory IgA

S IgA is a unique immunological feature of the gut mucosal immune system. Its primary function is specific defense against pathogens and toxins. Further S IgA antibodies have shown to establish and maintain healthy gut microflora. In relation to allergic condition, there is evidence that a reduction in S IgA levels is involved in allergy development. Low levels of salivary and intestinal S IgA are associated with an increased risk of allergic manifestations during early life. In mice, allergen sensitization using bovine lactoglobulin reduces intestinal allergen-specific S IgA levels and the number of IgA-producing cells in PPs compared with those in actively tolerized mice. S IgA may contribute to immune exclusion to reduce allergen uptake, but the mechanism by which S IgA protects against food allergy needs further study. Because commensal bacteria are critical mediators of oral tolerance, the interaction between S IgA and commensal bacteria is an issue of interest given its association with a reduction in allergy development. Children developing allergic manifestations—particularly asthma—during childhood have a lower proportion of IgA bound to fecal bacteria at 12 months of age than do healthy children. S IgA may limit the overgrowth of selected or undesired species, thus enabling an increase in microbial diversity in infancy followed by the induction of oral tolerance.

As an initial step to evoke the production of specific S IgA in the gut, pathogens, commensal bacteria, and antigens must be transported across the epithelial barrier into the GALT, including PPs, the gut, pathogens, commensal bacteria, and antigens must be transported across the epithelial barrier into the GALT, including PPs, the center court for the initiation of antigen-specific immune response in the gut, are seen as dome-like structures located in the small intestine opposite the mesentery (Fig. 1). Histologically, they consist of the follicular B-cell-rich areas and interfollicular T-cell-rich areas covered with follicle-associated epithelium containing M cells specialized for antigen sampling (Fig. 1). Antigen-presenting cells (APCs) such as dendritic cells (DCs) are present in the subepithelium and in the interfollicular zones in the PPs. In follicle-associated epithelium, pathogens or antigens are taken up by the M cells, which form intraepithelial pockets specialized for the
trans epithelial transport of antigens by macro molecular transcytosis to APCs. M cells can sample microorganisms and/or macromolecular antigens non-specifically (or engulfing capacity), they can also take up specific bacteria possessing FimH adhesin, such as Escherichia coli and Salmonella enterica, via glycoprotein 2 expressed on their apical membranes.

Following antigen uptake by the M cells, APCs such as DCs beneath the M cells capture the antigens, which are then processed and presented peptide-MHC complex to naïve CD4+ T cells. PP DCs produce IL-10 and induce the differentiation of Th2 cells. Activated T cells secrete the IgA inducing cytokines such as transforming growth factor β (TGF-β) and IL-4 to promote the class-switching of B cells to produce IgA. Cytokines secreted by mucosal T cells (IL-4 and TGF-β) and epithelial cells (TGF-β) cooperate to promote the maturation of IgA-producing B cells. Further, IL-5 and IL-6 produced by Th cells assist IgA committed B cells to differentiate to IgA producing plasma cells. In a T-cell-independent pathway, PP DCs directly induce IgA production in B cells via the stimulation of PP DC-derived RA and IL-6. Furthermore, intestinal DC-derived RA enhances the expression of IL-17 and CD103 in DCs on T and B cells upon activation and imprints the cells with “gut-homing” specificity. Through gut-homing, the activated antigen-specific T and B cells migrate from PPs through the efferent lymphatics to the regional MLNs and then to the intestinal LP by way of the lymphatic ducts and blood circulation.

For the gut imprinting system, this trafficking of activated antigen-specific B and T cells from the blood to the intestinal LP is regulated by interactions of gut-homing molecules involving α4β7 integrin and CCR9. Small intestinal microvascular endothelial cells express mucosal vascular addressin cell adhesion molecule 1 (MadCAM-1), which binds to α4β7 integrin. In addition, the endothelial cells release CCL25, which binds to its receptor, CCR9, in this way, activated antigen-specific B and T cells expressing α4β7 integrin and CCR9 are attracted to the LP. In addition, epithelial cells produce CCL25, further attracting these immune cells to the LP region below the villous epithelium. In the presence of various cytokines, including IL-5 and IL-6 produced by Th2 cells, IgA-committed B cells differentiate into IgA-producing plasma cells in intestinal LP. Dimeric or polymeric IgA released from the plasma cells attaches to the polymeric Ig receptor (pIgR) located on the basolateral surfaces of mucosal epithelial cells; it is then transcytosed to the apical surface and sequestered into the mucus layer as SlgA. During transcytosis, a portion of the pIgR is cleaved off; the remaining portion (called the secretory component) stays attached to the IgA. Therefore, IgA, rather than IgG or IgM, is the predominant immunoglobulin isotype in most mucosal secretions. SlgA attaches to pathogenic microorganisms and toxins and blocks their access to the mucosal epithelial cells. Furthermore, M-cell-mediated reverse transcytosis of antigen—SlgA complex contributes to presentation and processing by antigen-presenting cells, leading to an adaptive immune response against the antigen. The above mechanisms inducing antigen-specific SlgA production in the gut have been used to develop mucosal vaccines against gastrointestinal infections. Injectable vaccines induce antigen-specific IgG serum antibodies, but they are less effective in stimulating the gut mucosal immune system and eliciting a pathogen-specific SlgA response in the gut lumen. In contrast, the delivery of vaccines across mucosal surfaces—such as by the oral route—effectively provides pathogen-specific mucosal immune responses in addition to systemic immune responses.

Although M cells and DCs in the PPs mainly play a crucial role in the induction of acquired immunity, alternatively, antigens can be taken up by intestinal villous M cells or epithelial DCs located in the small intestine. TLR2, -4, and -9-mediated MyD88-dependent signaling in epithelial cells promotes trans epithelial extension of the cellular processes of epithelial DCs to directly sample luminal antigens into the LP. LCs also contribute to IgA production by B cells: In the LP, CD11b+CD11c+ DCs expressing TLR5 induce the differentiation of naïve B cells into IgA-producing plasma cells in response to flagellin stimulation. Commercial bacteria, including the 100 trillion bacteria in the gut, are also key components in shaping up SlgA induction system. Generally, commensal bacteria reside on the surface of the gut lumen or the intestinal epithelium, but our recent studies have revealed that some commensal bacteria (e.g., Alcaligenes faecalis) inhabit the inside of the DCs in PPs and produce necessary signals for the activation of IgA production system via the unique LPS.

Induction of oral immune tolerance

Immune tolerance is sustained immune unresponsiveness to beneficial antigens and commensal bacteria. A healthy immune system is generally situated under tolerant or quiescent condition sustaining unresponsiveness to self-antigen, dietary antigens and commensal bacteria. Based on numerous laboratory findings in humans and animals, oral tolerance is identified as reductions or unresponsiveness in systemic delayed-type hypersensitivity, T-cell proliferation, and Th2-type cytokine production. Serum antibody responses—particularly IgE production and Th1-dependent IgG2a production—can also be suppressed. The mechanisms of tolerance induction involve multiple pathways, including 1) deletion of reactive T cells, 2) anergy of reactive T cells, and 3) induction of regulatory T cells at mucosal sites. The contribution of each suppression pathway to oral tolerance induction depends on the animal model and the type of antigen used.

Among these inhibitory pathways, Treg-mediated oral tolerance is well studied and established. Three groups of immune cells such as, CX3CR1+ macrophages, CD103+ DCs, and Treg cells have been shown to play a crucial role, and villous LP and MLNs are the main inductive sites for oral tolerance (Fig. 2). First, CX3CR1+ macrophages directly take up small or soluble antigens from the intestinal lumen by sending their cellular processes out into the lumen across the epithelial barrier. Then, the CX3CR1+ macrophages transfer the antigens to CD103+ DCs in the LP via gap junctions, which are intercellular communication processes expressed on CD103+ DCs and formed by membrane proteins such as connexin 43. To a lesser extent, goblet cells can serve as epithelial gateways for the uptake of small antigens; this uptake is driven by the interaction of acetylcholine and muscarinic acetylcholine receptors. These epithelial antigen sampling systems are in close interaction with CD103+ DCs for the processing and presentation of the captured antigens. After transfer of the antigens from the CX3CR1+ macrophages or epithelial cells, CD103+ DCs move from the LP to the MLNs in a CCR7+-corresponding chemokine CCL21-dependent process. The CD103+ DCs then stimulate naïve CD4+ T cells to differentiate into forkhead box P3 (Foxp3)-expressing antigen-specific Treg cells via the release of RA, TGF-β, and indoleamine 2,3-dioxygenase (IDO) (Fig. 2). First, CX3CR1+ macrophages directly take up small or soluble antigens from the intestinal lumen by sending their cellular processes out into the lumen across the epithelial barrier. Then, the CX3CR1+ macrophages transfer the antigens to CD103+ DCs in the LP via gap junctions, which are intercellular communication processes expressed on CD103+ DCs and formed by membrane proteins such as connexin 43. To a lesser extent, goblet cells can serve as epithelial gateways for the uptake of small antigens; this uptake is driven by the interaction of acetylcholine and muscarinic acetylcholine receptors. These epithelial antigen sampling systems are in close interaction with CD103+ DCs for the processing and presentation of the captured antigens. After transfer of the antigens from the CX3CR1+ macrophages or epithelial cells, CD103+ DCs move from the LP to the MLNs in a CCR7+-corresponding chemokine CCL21-dependent process. The CD103+ DCs then stimulate naïve CD4+ T cells to differentiate into forkhead box P3 (Foxp3)-expressing antigen-specific Treg cells via the release of RA, TGF-β, and indoleamine 2,3-dioxygenase (IDO) (Fig. 2).
from microvascular endothelial cells in the small intestinal LP. This results in the homing of effector Treg cells to the small intestinal LP, where they create downregulatory condition in order to avoid unnecessary active immune status. Further, antigen-specific Treg cells are expanded in the LP in response to IL-10 released from CX3CR1 high macrophages (Fig. 2). Vitamin B is a factor that promotes the survival of gut Treg cells via the vitamin B9 receptor (folate receptor 4). 

Antigen uptake by mucosal DCs axis of villus epithelium-LP-MLN cascade is important for the induction of oral tolerance to soluble antigens in the small intestine. Further, PPs have been shown to involve in oral tolerance induction in the small intestine. M-cell-targeted antigen delivery has been thus reported to induce oral tolerance. However, oral tolerance is inducible even in the absence of PPs. Using PP-null mice model, it was shown that oral tolerance to hapten was induced and maintained. While oral tolerance against OVA protein was altered with exacerbated elevation of Th2 cytokines after OVA challenge. A current concept is that the amount or nature of the antigen (e.g. soluble, small, or particle), or both, determines its route of uptake into the different parts of mucosal tissue (LP or PPs) for the induction of oral tolerance. Particulate materials and microbiota mostly enter into the GALT by M-cell-mediated transcytosis, whereas soluble or small antigens induce oral tolerance after being absorbed by epithelial cells and/or taken up epithelium associated macrophages, DCs or goblet cells, and to a lesser extent, the GALT. Therefore, PPs might play a subordinate role in oral tolerance to proteins.

Evidence is accumulating that dietary antigen is critical in the induction of Treg cells in the small intestine but not in the colon, whereas commensal microbiota play a more important role in the induction of Treg cells in the colon than in the small intestine. In antigen-free mice that experience no exposure to any antigens, the number of Treg cells in the small intestine is significantly lower than in germ-free mice. However there is no significant difference in the number of Treg cells in the colonic mucosa between antigen-free and germ-free mice. On the other hand, when dietary antigens are ingested during weaning, Treg cells are produced in dramatic numbers in the small intestine to positively suppress the immune response to ingested dietary antigens. In germ-free mice, the numbers of Treg cells are reduced in the LP of the colonic mucosa, but when these mice are colonized with Clostridium species—commensal bacteria—Treg cells are produced in the colonic mucosa. This production is mediated by butanoic acid, a product of anaerobic fermentation. Polysaccharide A on the outer membrane of Bacteroides fragilis is recognized by TLR2 on CD4+ T cells and activates a signaling cascade involving myeloid differentiation primary response protein 88 and the induction of Treg-cell differentiation in the colon (Fig. 3).

Disruption of gut mucosal immune system leads to allergic inflammation

Disruption of a passage of the induction and regulation machinery necessary for oral tolerance induction discussed above leads to mucosal inflammation. CD103+ DCs producing IDO drive Foxp3+ Treg development, whereas inhibition or genetic deletion of IDO accelerates Th1 and Th17 differentiation and exacerbates colitis. RA, a metabolite of vitamin A, is crucial for the induction of Treg differentiation and gut homing receptors (e.g., CCR9 and α4β7); therefore, when mice are deficient in vitamin A, the numbers of α4β7-positive T cells in PPs and MLNs are reduced. As a consequence, antigen-specific T cells are unable to migrate from mucosal inductive sites (e.g., PPs) to effector site (e.g., LP), leading to an absence of Treg cells and effector T cells in the effector tissues. In addition, oral tolerance is abrogated by disruption of the gut-homing properties of Treg cells in β7-integrin- and MadCAM1-
deficient mice. Mice deficient in CCR7, which is required for CD103+ DC trafficking to MLNs, have impaired oral tolerance induction. CX3CR1 is a key molecule on CX3CR1-expressing macrophages in the transfer of antigens from the lumen to CD103+ DCs and for Treg proliferation in the intestinal LP via IL-10 production; deficiency of CX3CR1 results in reduced production of IL-10 in those macrophages, leading to impaired local Treg-cell proliferation. Loss of function in mucosal Treg cells results in severe inflammatory phenotypes in the lungs in addition to intestine.

Destruction of commensal bacteria is also a crucial factor in the failure of oral tolerance induction and in the development of allergic inflammation. Depletion of commensal bacteria by oral antibiotic treatment increases serum IgE concentrations; it also increases steady-state circulating basophil populations and exacerbates basophil-mediated Th2-cell responses and allergic inflammation. In conditions of continuous good health, microbial symbiosis limits naive CD4+ T cell differentiation into the effector T cells including Th1 and Th17 cells while promotes the induction of IL-10 production of CX3CR1+ macrophages and Treg cells. However, when the dysbiosis is occurred, CX3CR1+ mononuclear phagocytes shift the T-cell differentiation to pathogen-specific Th1-cell proliferation, thus inducing mucosal inflammation. Goblet cells have been shown to possess a capacity of antigen passage from the lumen to LP (Goblet cell-mediated antigen passage system), however its activity is suppressed in the colon by the colonic microbiota. On the other hand, antibiotic depletion of the microbiota leads to the activation of goblet-cell-mediated antigen passage, which accelerates the delivery of luminal antigens to both CD103+ and CD103- APC in the colonic LPs. This results in the production of inflammatory cytokines (e.g., IL-6 and IL-17) and chemokines (e.g., CXCL1) and an influx of leukocytes, including neutrophils, reflecting a state of acute inflammation.

In IgE-dependent food allergy, intestinal mast cells play an critical role in exacerbating allergic inflammation and symptoms (e.g., diarrhea) via chemical mediators such as histamine released by mast cells bound with the allergen-IgE complex (Fig. 3). In a model of OVA-induced allergic diarrhea, our previous study showed that sphingosine 1-phosphate (S1P) is responsible for the trafficking of pathogenic Th2 and mast cells. Our recent study further extended our knowledge of the mechanisms of mast-cell-mediated intestinal inflammation: Mast cells promote intestinal inflammation via the interaction of extracellular ATP and P2X7 purinoceptors; this pathway is effectively inhibited by P2X7 purinoceptor-specific antibody. Accumulated evidence has revealed that ATP-P2X7 pathways enhance IgE-mediated degranulation of mast cells in an autocrine and paracrine manner.

Preventive and therapeutic approaches to allergic inflammation

Studies are now using accumulated evidence on the gut mucosal immune system to develop preventive and therapeutic approaches to allergy. In a model of OVA-induced allergic diarrhea that has been established in our group, Th2-dominant environment accelerates diarrhea; therefore, an immunotherapy aimed at inhibiting the Th2-type response has been considered. In our previous study, intranasal administration of IL-12p70 naked DNA expression plasmids resulted in the synthesis of corresponding cytokines in large intestinal CD11c+ DCs; this inhibited the antigen-specific Th2-type response, preventing OVA-induced allergic diarrhea and suppressing clinical signs and symptoms, including OVA-specific IgE synthesis. The murine model of OVA-induced allergic diarrhea is associated with infiltration by mast cells and pathogenic CD4+ T cells; trafficking of both of these types of cells is promoted.
by 1S.100 On the basis of this finding, we further demonstrated that FTY720, a modulator of the 1S receptor, protects against allergic diarrhea by inhibiting the migration of systemically primed pathogenetic CD4+ T cells and mast cells in the colon.100

The concept of oral tolerance induction is also being applied to the prevention of pollinosis. Oral administration of genetically modified edible rice seeds, containing the major T-cell epitopes derived from cedar pollen allergens, induces oral immune tolerance to pollen protein and thus reduced allergen-specific IgE levels, T-cell proliferative reactions, histamine production, and allergy symptoms.104Nutritional approaches have been explored to treat allergic diarrhea. A metabolite of dietary ω3 polyunsaturated fatty acids, 17,18-epoxyeicosatetraenoic acid, reduces OVA-induced allergic diarrhea by inhibiting mast cell degranulation in the colon via an IgE-independent pathway.104 The importance of vitamins A and B in inducing and maintaining Treg cell implicates the utility of healthy commensal bacteria leading to the reduction of Treg cells of the pathological disturbance of the induction and maintenance of gut homeostasis, as described in murine models.42 Therefore, further study is needed to determine the usefulness, doses, and timing of vitamin use in terms of food allergy onset.

Commensal bacteria are critical in inducing oral tolerance and maintaining gut homeostasis, as described in murine models.42 This suggests that the use of probiotics or prebiotics, or both, may reduce the incidence of allergic diseases in children.106,107 but currently the evidence is insufficient for recommending their use during pregnancy or infancy for this purpose.9,108 Another aspect of commensal bacteria is their destruction of symbiotic condition by the excess use of antibiotic has been suggested in association with allergic diseases in children.109,110 Antibiotic use during early life—especially multiple antibiotic uses—increase the risk of allergic diseases, including food allergy, in children.109,110 possibly because of the pathological disturbance of the induction and maintenance of healthy commensal bacteria leading to the reduction of Treg cells which result in the enhanced allergic sensitization.45 This evidence suggests that appropriate use of antibiotics is desirable for preventing allergic diseases in children. Verification by further studies in humans will influence the guidelines for allergy prevention.

Conclusions

The gut mucosal immune system maintains homeostasis through an ingenious network including such factors as GALT, immune cells of innate and acquired types, chemokines, and cytokines. External environmental factors such as commensal bacteria, vitamin A and metabolites participate in the construction of this unique gut mucosal homeostatic network. Disruption or deficiency of the components of the gut mucosal immune and homeostatic network lead to the impairment of oral tolerance, SlgA production, and mucosal barrier formation, eventually promoting allergen sensitization and allergic inflammation. Elucidation of the mechanisms creating and disrupting the intestinal mucosal immune and homeostatic network is key to the development of preventive and therapeutic approaches to allergy. Further studies exploring these mechanisms are critical.

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