

Regulation of IgE Production and Other Immunopathogenetic Mechanisms

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Introduction

Adverse reactions to food may be caused by food allergy or food intolerance. Food allergy is the result of abnormal immunologic responses after ingestion of food. The typical form is an IgE-mediated type I hypersensitivity reaction to antigens present in food or food additives. Food intolerance is not immunologically mediated and possibly makes up most of the reported adverse reactions to food. Food intolerance may be from various causes like presence of toxic contaminants in ingested food (e.g., histamine in scombroid fish poisoning), pharmacologic properties of the food (e.g., tyramine in aged cheese), metabolic deficiency of the host (e.g., milk intolerance owing to lactase deficiency), or idiosyncratic responses of the host. The prevalence of allergy is difficult to establish because of lack of uniformly followed terminology, of objective challenge techniques to confirm diagnosis, and of supporting laboratory data to confirm involvement of the immune system. In infants and children, the incidence of food allergy is reported to be between 1 and 2%, and the prevalence decreases as children get older (1).

IgE plays a central role in the pathogenesis of allergic diseases including food allergy. IgE is regulated by various cytokines produced by T-cells and other cells. The gastrointestinal mucosa also regulates the production of food-specific IgE through local control mechanisms. In this article, the pathophysiologic mechanisms of food allergy and regulation of IgE production are discussed.

Pathogenesis of Food Allergy

Oral Tolerance

The main function of the gastrointestinal tract is to process ingested food into absorbable form. During the process, physiological and immunological barriers operate to block pathogenic foreign antigens from entering the body. In infants, immaturity of these mechanisms reduces the efficiency of the barriers. The main immunological barrier to foreign antigens is provided by the gut-associated lymphoid tissue (GALT). GALT is composed of aggregates of lymphoid follicles present throughout the intestinal mucosa as Peyer's patches and the appendix, scattered lymphocytes and plasma cells in the lamina propria, intraepithelial lymphocytes interdigitated between enterocytes, and the mesenteric lymph nodes (2,3). In children and adults, intact food antigens penetrate the gastrointestinal tract and enter the circulation. However, intact antigens entering the circulation does not cause clinical symptoms because normal individuals develop tolerance to ingested antigens. It was believed that the gastrointestinal tract of food allergic infants were more permeable to macromolecules than those of normal or older subjects. However, studies quantitating the amount of absorbed antigen do not show any differences between food allergic and normal subjects (4,5).

Immunologically intact protein entering the circulation does not normally cause clinical symptoms because most individuals develop tolerance to ingested antigens. The tolerance most likely develops at GALT, however, the mechanism by which tolerance develops in humans is not well understood. Experiments in mice show that the lymphoid cells are important in the development of tolerance. Irradiated mice lose their ability to develop tolerance to ovalbumin, which is restored by the infusion of normal spleen cells (6). Activation of a population of CD8⁺ "suppressor cell" may be important in the development of tolerance as depletion of these cells by cyclophosphamide treatment in mice prevents the development of tolerance to ovalbumin (7). Also, mucosa-induced tolerance can be transferred adoptively with purified T-cells from tolerized animals, in particular by cells expressing the CD8⁺ phenotype (8). Such transfer of tolerance can be inhibited by using blocking antibodies against interferon- γ (IFN- γ) and transforming growth factor- β (TGF- β) (9,10). Antigen-presenting cells (APCs) in the gastrointestinal tract may also play a role in the development of tolerance (11).

Immunological immaturity of infants also plays a role in the development of food allergy. The newborn lacks IgA and IgM in exocrine secretions, and salivary secretory IgA levels are very low during the early months of life (12). The low concentration of secretory IgA in

the intestine of infants, with the large load of ingested proteins, contributes to the excessive amount of food antigens confronting the immature GALT. In genetically predisposed infants, these antigens may stimulate excessive production of food-specific IgE antibodies. Several prospective studies have suggested that exclusive breast feeding and maternal antigen avoidance during pregnancy and lactation may promote the development of oral tolerance and prevent development of allergies like atopic dermatitis (13,14). The protective effect may be the result of decreased exposure to foreign proteins, breast milk secretory IgA, and soluble factors in breast milk that may induce earlier maturation of GALT and the immune response.

Immunologic Mechanisms

In high-risk infants, a breakdown in the development of oral tolerance results in hypersensitivity responses to ingested food antigens. Classic responses are caused by IgE-mediated type I hypersensitivity reaction. The IgE is specific for the food antigen. These antibodies bind to high-affinity FcεRI receptors on mast cells and basophils. On re-exposure, food allergens reach these sensitized mast cells and basophils and crosslink the IgE molecules. This results in a cascade of intracellular events leading to the rapid release of histamine and other preformed mediators present in mast cell and basophil granules. These mediators cause the manifestation of the immediate hypersensitivity reaction. The activated cells also release cytokines and other inflammatory mediators, which cause the IgE-mediated late-phase response. The clinical manifestations of food allergy are the result of these immunologic reactions (15). IgE is therefore the key element in the development of food allergy.

Control of IgE Synthesis

The level of IgE in body fluids is very low and does not vary much in healthy individuals. Even in highly atopic individuals, the levels of IgE to specific allergens are typically <100 ng/mL (16). These low levels suggest that IgE antibody production is regulated tightly. Experiments in mice provided some earlier clues to the factors involved in IgE regulation. In mice, two types of regulation were defined (17,18). First, some strains of mice make higher IgE in response to immunization with antigens than other strains. This IgE response parallels the IgG response and is regulated by major histocompatibility complex (MHC)-linked immune response genes. Second, some strains produce no IgE (SJA/9) or very low levels (AKR, SJL) of IgE despite good IgG response. The low responses are not MHC linked. Based on x-irradiation and cell transfer experiments, it was suggested "suppressor T-cells" were regu-

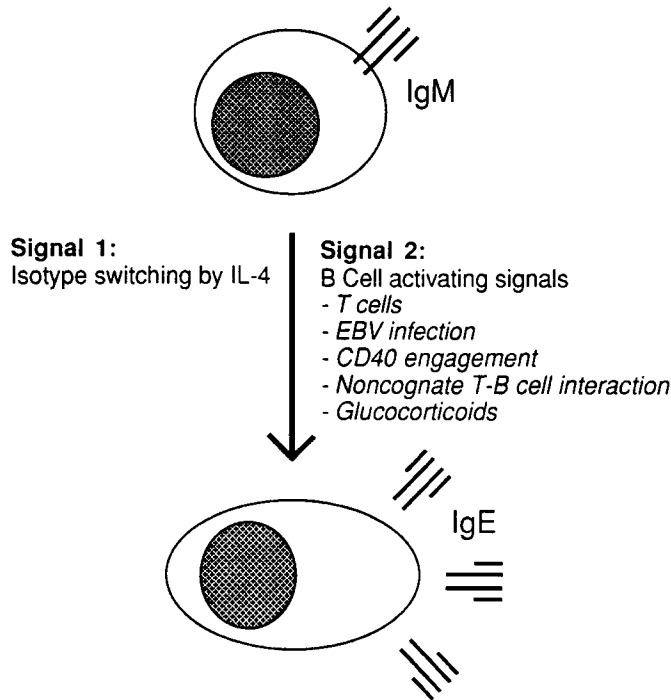


Fig. 1. Two-signal model for the induction of IgE synthesis.

lating IgE antibody responses (19). More recent data suggest that the cytokine IFN- γ produced by T-cells were suppressing IgE production (20). Subsequent studies in mice and humans have shown that the induction of IgE synthesis is highly T-cell dependent. One important component to such dependence is the T-cell cytokine interleukin-4 (IL-4). The other components are T-cell stimulatory events that induce competence for switching, although these are not class specific.

Recent evidence suggests that induction of IgE synthesis in humans requires two signals (21). The first is delivered by the cytokine IL-4 which is IgE isotype specific. The second includes events that can be grouped as B-cell-activating signals (Fig. 1). In subsequent sections these two signals are discussed.

Isotype Switching by IL-4

The antigen-binding specificity of immunoglobulin molecule is determined by the amino-terminus of the heavy and light chain, which is highly variable. The effector functions of the molecule are determined by the carboxy-terminus of the heavy chain which is constant and class specific. The variable region of immunoglobulin is encoded by multiple germ-line elements assembled into V(D)J regions during B-cell

differentiation by enzymatic recombinase activity encoded by the RAG-1 and RAG-2 genes (22,23). During an immune response, a B-cell can express different heavy-chain isotypes sharing the same V(D)J region. Class switching results from a recombination event that juxtaposes a heavy-chain gene to the V(D)J gene. Intervening sequences, including the previously expressed heavy-chain genes, are deleted.

Recent studies have identified that IL-4 is the crucial factor for isotype switching to IgE. The role of IL-4 in the induction of IgE first became evident when it was shown that recombinant IL-4 could induce IgE production by lipopolysaccharide (LPS)-stimulated murine B-cells (24,25). More recent studies in mice and human B-cells have shown that IL-4 by itself is sufficient to activate transcription through the ϵ locus (26–28). In vivo and in vitro studies in the mouse support the view that IL-4 is absolutely required to generate an IgE response and no other cytokine has been able to substitute for IL-4. Mice in which the IL-4 gene has been disrupted by gene targeting have no serum IgE and fail to make IgE in response to immunization. Such animals also have a striking, but not total, reduction in serum IgG₁ levels (29,30). In humans, IL-13, a close congener of IL-4, can also cause immunoglobulin class switching to IgE (31). The relative importance of these two cytokines in the human physiology of switching to IgE expression has not been established.

On theoretical grounds, IL-4-induced switching to IgE (VDJ-CH ϵ transcript) can occur by one or more of the following mechanisms: deletional switching (28), splicing of long RNA transcripts (32), or transsplicing (33). Evidence favors deletional switching to be the likely mechanism in B-cells (34). IL-4-mediated switching is associated with the induction of transcription at a site upstream of the switch region for IgE (S ϵ). The region is termed I ϵ . The initial immature transcript I ϵ S ϵ C ϵ is later spliced to a more mature transcript I ϵ C ϵ (34,35). This transcript possibly does not encode a functional protein. The transcription at I ϵ site possibly opens the chromatid in the downstream S ϵ site allowing for the recombination events to occur resulting in deletional switching and transcription of mature VDJ-CH ϵ (28).

B-Cell Activating Signals

Although IL-4 is sufficient for the germ-line transcription through the ϵ locus of immunoglobulin gene, additional signals are required for the expression of mature ϵ mRNA and subsequent IgE synthesis by B-cells. Highly purified B-cells cannot be induced to produce IgE by IL-4 alone. In mice, addition of LPS to the B-cell culture can restore the production of IgE (35). In humans, addition of T-cells can restore the ability of B-cells to produce IgE (36). These experiments show that in

addition to IL-4, a second signal is required for production of IgE (Fig. 1). The signals that synergize with IL-4 in the induction of IgE are discussed in the following sections.

T-Cells

T-cells are crucial for IgE induction not only as a source of IL-4, but also because of their ability to deliver a second signal to B-cells following cognate interaction between the T-cell receptor/CD3 complex on the CD4⁺ helper T-cells and the MHC class II antigens on B-cells presenting the antigenic peptide. This antigen-specific T-B-cell interaction activates both T- and B-cells (36). T-cells produce other cytokines like IL-5 or IL-6 which supports IgE production, and IFN- γ which inhibits IgE production. The balance between the T-cells subsets producing cytokines having opposing effect on IgE production by B-cell may ultimately determine whether an IgE response to an antigen will be generated or not. Established T-cell clones from atopic individuals support the concept that repeated and chronic antigenic stimulation by allergens selects for allergen-specific T-cells that polarize to a type that produces large amounts of IL-4, IL-5, IL-6, and low amounts of IFN- γ (37,38). These T-cells would support production of larger amounts of allergen-specific IgE. Cytokine control of IgE secretion is discussed further in a subsequent section.

Epstein-Barr Virus (EBV)

EBV is an important regulator of IgE synthesis. The high incidence of EBV infection in children makes it relevant to the development of allergies to food and airborne allergen. Clinicians are familiar with the observation of precipitation or aggravation of allergies following viral infections. In vitro studies show that purified human B-cells in culture can be induced to produce IgE in the presence of IL-4 and EBV. This IgE synthesis is T-cell independent. The production of IgE is from *de novo* induction of isotype switching rather than from expansion of a pre-committed B-cell population (39,40). IgE production induced by IL-4 and EBV is derived from B-cells that have undergone EBV transformation, since all cells secreting the IgE express the markers of EBV infection EBNA-1 and EBNA-2 (40). IL-4 by itself is known to induce germ-line ϵ transcripts by normal B-cells, whereas mature C ϵ transcripts are only detected after stimulation with both IL-4 and EBV. This is consistent with the two-signal model for isotype switching to IgE. EBV delivers an activating signal functionally similar to LPS in the mice system. The nature of the EBV-induced signal in B-cell is not currently known. Viral proteins or cellular proteins produced by the infected B-cells are likely to be involved in the generation of the second signal. Another interesting possibility arises from the observation that expres-

sion of some latent EBV proteins protects human B-cells from programmed cell death or apoptosis (41). It is possible that IL-4 signal induces the switch to IgE production and the EBV-activating signal allows the B-cell to survive for a long period for the switching to become evident.

CD40 Engagement

CD40 is a cell surface glycoprotein expressed on B-cells and certain carcinomas and melanomas. The CD40 gene is related to the receptors for TNF- α and nerve growth factor. The ligand of CD40 (CD40L) is gp39 present on T-cells. The CD40-CD40L interaction between T- and B-cells is involved in B-cell activation and growth. An anti-CD40 monoclonal antibody (MAb) delivers a progression signal to resting B-cells in the presence of primary activators like phorbol esters (42). In purified human B-cells, anti-CD40 MAb in combination with IL-4 induces large amounts of IgE synthesis. Stimulation of B-cells with anti-CD40 MAb alone results in only modest IgG synthesis, but no IgE synthesis. Thus, the synergism between IL-4 and CD40 engagement results primarily in the induction of IgE synthesis (43,44). The importance of CD40 signaling in immunoglobulin class switching is further shown by the recent observation that in a form of human immunodeficiency syndrome called x-linked hyper-IgM, the CD40L gene is mutated (45,46). In these patients, cognate interaction between CD40L on activated T-cells and CD40 on responsive B-cells does not occur because of the mutation. Therefore, the switch from IgM to other immunoglobulin classes is defective. These patients have a high IgM level and very low levels of IgE and other immunoglobulin classes.

Noncognate T-B-Cell Interactions

In addition to cognate T-B-cell interactions, noncognate T-B-cell interactions may provide a second signal for induction of IgE synthesis. Phytohemagglutinin (PHA)-induced T-cell clones are reported to induce IgE synthesis by human B-cells from randomly selected donors in presence of exogenous IL-4 (47). Mouse thymoma cells induce human B-cells to produce IgE in presence of phorbol esters and exogenous human IL-4 (48). In both experiments, importance of cell-cell contact is shown by culturing T- and B-cells in chambers partitioned by semi-permeable membranes. The importance of these models in *in vivo* IgE production is not clear at this time.

Glucocorticoids

Studies have shown that hydrocortisone in combination with IL-4 can induce IgE production in B-cell lines and in normal polyclonal B-cells in the absence of T-cells and monocytes (49-51). The effects of

Table 1
Features of Murine Th1- and Th2-Subsets of T-Helper Cells

	Th1	Th2
Cytokines produced	IL-2, IFN- γ , TNF- β , IL-3, GM-CSF	IL-4, IL-5, IL-6, IL-10, IL-13, IL-3, GM-CSF
Cell types activated	Macrophages	B-cells, eosinophils, mast cells
Inflammatory reactions	Cell-mediated immunity Delayed-type hypersensitivity	Humoral immunity Allergic reactions

glucocorticoids are specific since other steroids like sex steroids do not influence the IL-4-dependent IgE synthesis. Glucocorticoids also increase in vivo production of IL-4 (52). The mechanism of hydrocortisone and IL-4 synergism in IgE production is not known. The observation that glucocorticoids and IL-4 interaction can provide a signal for IgE synthesis is clinically relevant in view of the common use of steroids in treating allergic diseases.

Cytokine Regulation of IgE Production

Cytokines derived from T-cells are major modulators of IgE synthesis. T-helper (Th)-cell regulation of IgE synthesis has been studied extensively in mice. The magnitude and duration of IgE responses are largely determined by the interplay between two cytokines: IL-4 which increases IgE production, and IFN- γ which suppresses IgE production. The balance between the two is a key determinant in the in vivo expression of IgE (53,54). In the mouse, these cytokines are produced by distinct Th-cell subsets derived from naive T-helper cell (Th0) precursors. Th0-cells are thought to produce mainly IL-2 on initial encounter with antigen. On antigen priming, Th0-cells develop into cells that produce either IFN- γ or IL-4, which is described as Th1- or Th2-like effector cells, respectively. Th1-cells retain the capacity to produce IL-2, whereas Th2-cells do not. In mice, these two subsets have relatively restricted profiles of cytokine production and function (Table 1). Th1-cells secrete mainly IL-2 and IFN- γ , and are the principal effectors of cell-mediated immunity and delayed-type hypersensitivity reactions. In contrast, Th2-cells elicit IgE production (by IL-4 and, possibly, IL-13), eosinophilic inflammation (by IL-5), and limit macrophage activation because they do not produce IFN- γ and also because two Th2-derived cytokines, IL-4 and IL-10, antagonize the macrophage-activating actions of IFN- γ . Th2-cells are effectors of antibody-mediated phagocyte-independent host defense against certain parasites and in allergic reactions (55,56).

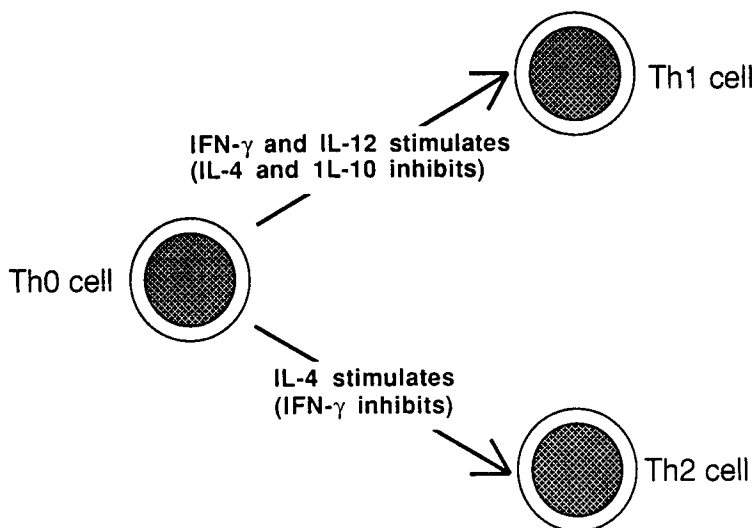


Fig. 2. Induction of different subsets of Th-cells by cytokines.

In humans, it is likely that a similarly biased distribution of cytokine profiles exists among the Th-cell subsets (57,58).

The factors that play major roles in driving Th0-cells toward the Th1- or Th2-phenotypes are cytokines and APCs. The nature and route of antigen exposure may also play a role. The cytokines that are produced early after antigen exposure and that T-cells encounter during their differentiation influence which subset is mainly induced (Fig. 2). IFN- γ and IL-12 promote the development of Th1-cells. In contrast, IL-4 stimulates differentiation toward Th2-cells (56). Of the APCs, activated macrophages are potent at stimulating differentiation along the Th1-pathway, in part because they are major sources of IL-12 (59).

In addition to the development of Th2-phenotype as described, variety of other cytokines produced by T-cells and other cell populations also play important roles in IgE production. IL-12 and IFN- α from mononuclear phagocytes, and IFN- γ from natural killer (NK) cells and CD8⁺ T-cells downregulate IgE production by selecting the growth of Th1-cells (60,61). IL-13 produced by Th2-cells acts similar to IL-4 in promoting IgE synthesis (31,62), and this pathway is amplified by Th1-suppressive effects of Th2-cytokine IL-10. IL-6 enhances IgE production by acting at a relatively late stage of B-cell maturation (63). IL-5 enhances IgE production when B-cells are cultured with IL-4 (64). TGF- β indirectly inhibits Th2-cell proliferation by amplifying the production of IFN- γ by CD8⁺ T-cells (65).

Interestingly, the genome of EBV contains a gene homologous to IL-10. The viral IL-10 homolog shares in vitro activity with the IL-10 produced by T-cells (66). This raises the possibility that the virus has

the IL-10 function to suppress Th1-response and antiviral immunity and stimulate the Th2-response. The change in Th1- and Th2-balance will favor IgE production.

IgE Response to Antigens

Immune responses to antigens impinging on the mucosal surfaces are under local and systemic control. Although the range of cytokines and other immunological mechanisms discussed undoubtedly play an important role in the regulation of the immune response including IgE production and allergy, the precise mechanism is still speculative. The mucosal surfaces of interest in atopic disease are the gastrointestinal tract and respiratory tract. The gastrointestinal tract is particularly faced with the problem of large antigenic load and the continuous need to discriminate between antigens which need to be ignored as ubiquitous nonpathogenic antigens, and antigens associated with potential pathogens that merit vigorous immune response. Failure of this would be catastrophic. Also, inappropriate response to ubiquitous antigens like food antigens lead to development of food allergies (15).

The "default" immune response to food antigens in the normal host is the generation of a state of antigen-specific hyporesponsiveness, which is known as oral tolerance. Of the antibody responses, IgE response is tolerized most readily and the hyporesponsiveness is most stable. Antibody responses of other isotypes are preserved to a variable degree (67). Low concentrations of food-specific IgG, IgM, and IgA antibodies are commonly seen in the serum of normal individuals, which are usually of no clinical significance (68).

Antibody response of IgG and IgE isotypes to aeroallergen and food antigen during infancy and childhood follows a typical pattern. The IgG response persists, whereas the IgE response is turned off after a transient response. All children initiate IgG response to aeroallergens by 3 mo of age, which is of the IgG₁ subclass (69). This response persists into adulthood when they are usually accompanied by an IgG₄ response (70,71). IgG₁ production against food allergen is also common in infants and is accompanied by a specific IgG₄ response from the outset (71). In normal children, IgE response to aeroallergen is usually seen after 1 yr of age, peaking at about 4 yr of age, and decline to very low level in the next 4 yr. In contrast, in atopic children, the IgE antibody titer rises more rapidly, peaks at a higher level, and in most of the children the high titer is maintained for long time (67,72). Food allergen-specific IgE response occurs earlier. Initial response is seen usually at 3–6 mo of age. The level peaks by the age of 1 yr, then declines in most children within the next 2–3 yr (72,73). In atopic children the level remains elevated. In the normal situation, IgE response to food allergens is

Table 2
Features of IgE Responses to Environmental Allergens in Normal Children^a

	Aeroallergen	Food allergen
Exposure amounts	ng	µg-g
Initial appearance of serum IgE	1-2 yr	3-6 mo
Duration of transient IgE responses	3-5 yr	1-2 yr
Skin-test reactivity	+ in atopics	transient +

^aAdapted from ref. 67. Reproduced with permission. +, positive.

turned off more efficiently than inhalant allergens (Table 2). Food allergy is therefore less common than airway allergy. Even in highly atopic individuals, food-specific IgE is rarely seen. The mechanism of this efficient downregulation of IgE response in the gastrointestinal tract compared to the respiratory tract is not known. The larger antigenic load in the gut and differences in local APCs or immune responses may be important.

The transient IgE response to food allergens during infancy is possibly the phase of induction of oral tolerance. Environmental factors, particularly those associated with mucosal inflammation, may override this mechanism, converting the normally tolerogenic signal to a strong and permanent immunogenic signal. Animal experiments lend support to this concept. Oral feeding of ovalbumin to rats normally induce ovalbumin-specific oral tolerance, whereas feeding a strain of *Escherichia coli* expressing transfected ovalbumin gene in rats induces a strong antiovalbumin immunity (74). Ubiquitous environmental antigens, like food antigens encountered during inflammatory responses to microbial agents or chemical irritants in the mucosa, may convert an otherwise tolerogenic response to an immunogenic response in human and development of specific IgE production and allergies.

Development of specific IgE to food and other environmental allergens is likely to be controlled by the interplay of Th-cell subtypes and cytokines. A model for the development of allergies based on T-cell regulation of IgE production has been proposed recently (67). During infancy and childhood, encounters with ubiquitous food and airborne allergens trigger CD4⁺ T-cell subtypes involving Th0, Th1, and Th2, which leads to heterogeneous allergen-specific antibody responses including a low level of IgE production. During repeated stimulation from these environmental allergens, a selection process involving crossregulation of Th1- and Th2-cells possibly follows. In the natural process most of the individuals develop a dominant Th1-memory phenotype with waning of Th2-dependent IgE production. In people predisposed to develop allergy, the natural process possibly fails, leading to the emergence of Th2-phenotype with development of allergies including food allergy.

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