Review Article

Concurrent exposure to microbial products and food antigens triggers initiation of food allergy

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It is estimated that as much as 6-8% population suffers from food allergy or food antigen-related disorders. The prevalence keeps rising. So far we do not have identified remedy to treat food allergy. Avoidance of the offending food is the only effective method currently. Skewed T helper 2 polarization is one of the major feature in the pathogenesis of food allergy. However, the causative mechanism in the initiation of food allergy remains to be further understood. Research in food allergy has got giant advance in recent years. Several animal models have been established and used in food allergy study. One of the common features of these food allergy animal models is that most of them require using microbial products as adjuvant to sensitize animals. This review documents the recent advance in the mechanistic study on concurrent use of microbial products and food antigens to study food allergy. (Chen X, Yang PC. Concurrent exposure to microbial products and food antigens triggers initiation of food allergy. **North Am J Med Sci** 2009; 1: 2-8).

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Introduction

The aberrant Th2 immune response is believed to be a crucial feature of food allergy [1, 2]. The mechanisms of developing pathological Th2 responses remain unclear. In synergy with antigens, microbial derived adjuvant plays a critical role in developing allergic reactions in animal models [3-8] whereas the hygiene hypothesis proposes that the exposure to microbial products in early life prevents from allergic diseases with the mechanisms remained to be further elucidated [9-12]. Some researchers suggest that the opposing results may be due to the different exposure levels and if the exposure to microbial products is with a simultaneous antigen exposure [13-15]. Thus, it is possible that concurrent exposure to microbial products and food antigens up-regulates TIM4 (T cell immunoglobulin and mucin-domain-containing molecule 4) expression in the intestinal antigen-presenting cells (APCs); the interaction of TIM4 with TIM1 on naive CD4+ cells leads to Th2 immune polarization and thus facilitates the development of allergic reactions to food antigens. This review focuses on the recent published information to dissect the mechanism by which the synergistic effect of microbial products and food antigen triggers the initiation of skewed antigen specific Th2 responses and development of food allergy.

Gastrointestinal allergic reactions compromise human health and social economy.

As many as 4~8% of children and 1~2% of adults have the IgE-mediated hypersensitivity to food antigens [16, 17]. The prevalence of food allergy and related disorders has increased rapidly across the world in the last few decades [18]. Research in the area of food allergy has advanced greatly in recent years; however the pathogenesis of food allergy remains unclear [19].The symptoms of food allergy range from slight inconveniences to life-threatening anaphylactic shock reactions [17]. Food allergic reaction involves not only the intestinal tract, but other body systems such as the skin [20], the airway [21] and the cardiovascular system [22]. IgE-mediated food allergy is one of the causes of eosinophil accumulation in the gastrointestinal tract that is a common feature of numerous gastrointestinal disorders [23]. Since the food allergic disorders are common throughout the world, affecting the males and the females of all ages, races and all social classes, they certainly represent a substantial burden of morbidity and health service cost [24, 25].

Oral tolerance maintains the homeostasis in intestinal tissue

Oral tolerance, as characterized by Chase in 1946 [26], refers to a state of active inhibition of immune responses to an antigen by means of prior exposure to that antigen through the oral route. In animal models, oral tolerance appears to be a specific consequence of the immune environment in the intestine, which favors the generation of T regulatory cells [27, 28]. The mechanism of oral tolerance may involve either anergy/deletion of CD4+ T cells, or the induction of regulatory CD4+ T cells (Tregs) that produce immune suppressive cytokines interleukin 10 (IL-10) and/or TGFbeta [29, 30]. Such CD4+ Tregs include CD4+CD25+ cells [31,

32]. It is postulated that a breakdown in oral tolerance or a failure of induction of oral tolerance results in hypersensitivity to food antigens [33]. However, it remains unclear how the established oral tolerance breaks down or fails to develop.

Th2 polarization plays a crucial role in oral tolerance impairment and the initiation of intestinal sensitization

The etiology of food allergy remains unclear; a failure to develop or a breakdown in the maintenance of, oral tolerance may be responsible [27, 28, 34, 35]. The key feature of the disease is a T-helper type 2 (Th2)-predominant allergen-specific immune response, with the production of IgE antibodies specific for the food allergen [1]. Th2 cells are produced when type 2 dendritic cells present antigen to the T cell's receptor for antigen (TCR) [36]. Contrast to Th1 cells which release type 1 cytokines such as IFNγ, the major cytokines secreted by Th2 cells are Th2 cytokines IL-4, IL-5 and IL-13. These cytokines are of major importance because IL-4 and IL-13 induce the production of IgE by B cells [37]. T cell differentiation is a complex process that is regulated by a network of transcription factors [38], including transcription factors T-box expressed in T cells (T-bet) and GATA binding protein 3 (GATA3) that are considered as the master regulators of Th1 and Th2 differentiation, respectively [38, 39]. (Fig 1).

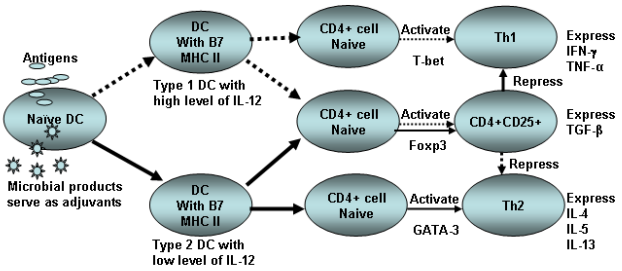

Fig 1. A simplified sketch of Th1/Th2 reactions development. Solid lines indicate that naïve APCs encounter antigens and microbial products (adjuvants) at the same time; broken lines indicate that APCs encounter either antigens or microbial products alone. APCs process antigen and/or adjuvant information together with MHC II and pass them to naïve CD4+ cells. Different transcription factors are activated under certain environment. Th1 or Th2 cells proliferate subsequently. CD4+CD25+ cells inhibit Th1 or Th2 reactions depending on to the different exposure levels and if the exposure to microbial products is with a simultaneous antigen exposure.

Role of SEB in allergic diseases

Staphylococcus aureus (*S. aureus*) is consistently found in human's intestine [40-42]. SEB is one of the enterotoxins produced by *S. aureus* that has multifaceted functions in the immune regulation [43-45]. SEB induces vigorous activation, proliferation, and cytokine production by T cells that express specific TCR variable beta (Vß) chains. Some investigators associate SEB with inducing the Th1 pattern inflammation [46-48], however, mounting evidence indicates that SEB is also involved in the pathogenesis of allergic diseases [43, 49-52] although the mechanisms have remained unclear. We and others have found that the simultaneous exposure to SEB and food antigens such as ovalbumin (OVA) enhances susceptibility to allergic reactions [43, 53-55]. SEB triggers immune cells to release the Th2 cytokines IL-4, IL-5 and IL-13 [55-58] and enhances antigen-specific immune responses [49, 59]. The primed T cells of antigen specificity would be further and more potently expanded by SEB [60, 61] while naive T cells of the same Vβ specificity would become anergized [62]. CD4+CD25+ Tregs play roles in suppression of the Th2 reactions [63-65]; however, in SEB-involved atopic patients, CD4+CD25+ Tregs demonstrate incompetent inhibitory capability in suppression of the Th2 reactions [66]. SEB would thus be a potent activator of both cellular and humoral arms of the immune system in an antigen-specific manner. SEB increases permeability of the intestinal epithelium leading to enhanced uptake of the co-administered antigen [53]. SEB also induces dendritic cell maturation that may enhance antigen presentation by APCs [67].

Adjuvants are required to induce sensitization in animal models

Adjuvants are substances that are added to vaccines or with antigens to improve the immune responses. Such adjuvants work by speeding the differentiation of lymphocytes. We induce intestinal sensitization in animal models using pertussis toxins/vaccines as adjuvants together with antigens ([3-6, 68-72]. Cholera toxins [1], Freund's adjuvant [73], etc are also commonly used with antigens in developing allergic animal models. Microbe-derived toxins or their components are commonly used as adjuvants. They more likely induce Th1 reactions if used alone [74, 75)] but enhance both Th1 and Th2 or Th2 reactions when used together with antigens [76, 77]. Similar to the adjuvants mentioned above, SEB has been shown to facilitate the development of either Th1 reactions [46-48] or Th2 allergic disorders [49-52].

Role of TIM1 and TIM4 in regulation of immune function

The family of TIMs has been described in the mice recently, and their homologous molecules have been identified in the human, monkey, and rodent [78]. TIM1 is encoded by a gene identified as an 'atopy susceptibility gene' (Havcr1) and is expressed on CD4+ T cells after activation. It is preferentially expressed in T helper type 2 (Th2) but not Th1 cells. TIM1 has been identified as being important in asthma and allergy susceptibility although it also associates with the hygiene theory because it is the receptor of the hepatitis A virus [79-82]. TIM1 plays an important role in the activation of Th2 cells and the inhibition of the peripheral tolerance [83, 84]. On the other hand, TIM4 is expressed by APCs; it is the ligand for TIM1. In vitro stimulation of CD4+ T cells with a TIM-1-specific monoclonal antibody and T cell receptor ligation enhanced T cell proliferation; in Th2 cells, such costimulation greatly enhanced synthesis of interleukin 4 but not interferon-gamma [83]. In vivo administration of either the soluble TIM1-immunoglobulin (TIM1-Ig) fusion protein or the TIM4-Ig fusion protein resulted in hyperproliferation of T cells, and TIM4-Ig costimulated T cell proliferation mediated by CD3 and CD28 in vitro. These data suggest that the TIM1-TIM4 interaction is involved in

regulating T cell proliferation [34]. Although SEB can bind to the TCR to activate T cells directly, SEB also promotes dendritic cell maturation as shown by increased expression of CD40, CD80 and CD86 [67]; Our previous study indicates that SEB also increases the TIM4 expression in the intestinal APCsand increase the histone acetylation at lysine 9 (an indicator of gene transcription).

Specific gaps in existing knowledge in the field of food allergy research

We know that antigens interact with immune cells and induce the immune reactions; it has been unclear what decides the outcome of immune reactions in the gut: immune-tolerance or hypersensitivity [16-18]. While the growing evidence indicates that SEB plays roles in the regulation of both Th1 and Th2 inflammation, the mechanisms have to be understood [46, 47, 50, 51]. Emerging evidence strongly suggests a critical role of the TIM1 and TIM4 interaction in regulation of Th1/Th2 balance [34, 35, 83, 84]. However, the role of TIM1 and TIM4 in the immune mechanisms of food allergy in the intestine has not been investigated. We have established a murine model of intestinal Th2 sensitization and food allergy by concurrent exposure to SEB (microbial product) and OVA (food antigen). By using this model system, we will investigate the role of TIM1 and TIM4 interaction in the immunopathogenesis of intestinal food allergy. Both in vitro and in vivo approaches will be used in our studies.

Recent advances

We recent found that a significant increase in TIM4 expression in human DCs was observed in response to SEB stimulation via Toll-like receptor (TLR)2 and nucleotide-binding oligomerization domain (NOD)1 pathway. Coculture SEB-conditioned DCs with naïve CD4 T cells induced Th2 responses that could be abolished using TLR2 or NOD1 or TIM4 or TIM1 with counterpart antibodies or RNA interference. The results demonstrate that Staphylococcus aureus derived SEB promotes the TIM4 production in human DCs. The interaction between TIM4 and TIM1 drives naïve CD4 T cells to develop to Th2 cells [85]. In another study, we determined the role of TIM-4, a recently identified member of cell surface molecules, in the pathogenesis of intestinal allergy in a murine model. We report that TIM-4 as well as costimulatory molecules were up-regulated in intestinal mucosal dendritic cells by in vitro or in vivo exposure to SEB. SEB-conditioned intestinal dendritic cells loaded with a food macromolecule ovalbumin (OVA) induced potent OVA-specific Th2 lymphocyte responses in vitro and such Th2 responses were inhibited completely by TIM-4 blockade. In vivo exposure to both SEB and OVA resulted in OVA-specific Th2 differentiation and intestinal allergic responses including increased serum immunoglobulin E and Th2 cytokine levels, activation of OVA-specific Th2 cells detected both ex vivo and in situ, and mast cell degranulation. Of importance, in vivo abrogation of TIM-4 or its cognate ligand TIM-1 by using a polyclonal antibody remarkably dampened Th2 differentiation and intestinal allergy. This study thus identifies TIM-4 as a novel molecule critically required for the development of intestinal allergy [86]. We have taken a further step in this series of study. In a project with animal model, mouse bone marrow-derived DCs (BMDCs) were generated and exposed to cholera toxin (CT) or/and peanut extract (PE) for 24 hours and then adoptively transferred to naive mice. After re-exposure to specific antigen PE, the mice were killed; intestinal allergic status was determined. The results showed that Increased expression of TIM4 and costimulatory molecules was detected in BMDCs after concurrent exposure to CT and PE. Adoptively transferred CT/PE-conditioned BMDCs resulted in the increases in serum PE-specific IgE and skewed T(H)2 polarization in the intestine. Oral challenge with specific antigen PE induced mast cell activation in the intestine. Treating with Toll-like receptor 4 small interfering RNA abolished increased expression of TIM4 and costimulatory molecules by BMDCs. Pretreatment with anti-TIM1 or anti-TIM4 antibody abolished PE-specific Th2 polarization and allergy in the intestine. We conclude that concurrent exposure to microbial product CT and food antigen PE increases TIM4 expression in DCs and promotes DC maturation, which plays an important role in the initiation of PE-specific Th2 polarization and allergy in the intestine. Modulation of TIM4 production in DCs represents a novel therapeutic approach for the treatment of peanut allergy [87].

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