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Epicutaneous sensitization. what do we know?

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ABSTRACT

Background. According to the currently existing hypothesis, epicutaneous sensitization is one of the leading mechanisms in the development of food allergy.

The aim of this review was to analyze immune mechanisms in epicutaneous sensitization and the role of skin barrier impairment.

We performed a literature search using PubMed, UpToDate, Web of Science, and Scopus databases by the key words: epicutaneous sensitization, atopic dermatitis, skin barrier impairment, food allergy. Articles were to be in open access and present the most relevant information on the topic. Studies were selected by the largest sample size and the highest citation index. Once publications were identified, they were reviewed by all the authors to select the studies that specifically addressed the theme of the review. A total of 101 publications from 1998–2000 were included in the study.

This review article discusses the data of experimental studies, sets out modern ideas about the hypothesis of a double exposure to an allergen, and presents research data proving the clinical significance of epicutaneous sensitization in relation to food allergy. Knowledge about the mechanisms of epicutaneous sensitization development is necessary to elaborate strategies for prevention of food allergy. One of the modern trends in prevention is the use of emollients, which are supposed to restore the skin response. However, studies on preventive intake of emollients do not present a similar viewpoint.

There is not enough evidence for or against the mechanism of epicutaneous sensitization as an indispensable condition for the formation of food allergies. Further research in this area is required.

Key words: epicutaneous sensitization, skin barrier impairment, food allergy, emollients, atopic dermatitis.

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Транскутанная сенсибилизация. Все ли мы знаем?

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РЕЗЮМЕ

Согласно существующей в настоящее время гипотезе, транскутанная сенсибилизация является одним из ведущих механизмов формирования пищевой аллергии.

Цель: анализ иммунологических механизмов формирования транскутанной сенсибилизации и роли дефекта кожного барьера.

Для написания обзора был проведен поиск полнотекстовых публикаций на английском языке в базах данных PubMed, UpToDate, Web of Science, Scopus по ключевым словам: epicutaneous sensitization, atopic dermatitis, skin barrier defect, food allergy. Статьи должны были находиться в свободном доступе и представлять наиболее актуальную информацию по теме. Исследования отбирались по принципу наибольшей выборки и индекса цитирования. После первичного отбора публикаций авторы изучили их на предмет соответствия информации тематике исследования. В обзор включена 101 публикация за период 1998–2020 гг.

Рассмотрены данные экспериментальных исследований, изложены современные представления о гипотезе двойного воздействия аллергена, приведены данные исследований, доказывающих клиническую значимость транскутанной сенсибилизации в формировании пищевой аллергии. Знание механизмов развития транскутанной сенсибилизации необходимо для выработки стратегий профилактики пищевой аллергии. Одним из перспективных направлений профилактики пищевой аллергии является использование эмолиентов, которые восстанавливают кожный ответ, однако исследования, посвященные профилактическому приему эмолиентов, в настоящее время не дают однозначного ответа.

В настоящее время накоплено недостаточно данных ни «за», ни «против» существования механизма транскутанной сенсибилизации как обязательного условия для формирования пищевой аллергии. Требуется дальнейшее проведение исследований в данном направлении.

Ключевые слова: транскутанная сенсибилизация, дефект кожного барьера, пищевая аллергия, атопический дерматит.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

The term “food allergy” refers to a pathological immune response that develops after a contact with food (usually a meal) [1, 2]. Currently, several types of food allergy are distinguished with differences in their pathophysiological mechanisms (IgE-mediated and non-IgE-mediated) and clinical manifestations.

Atopic dermatitis (AD) is considered to be one of the risk factors for the development of food allergy. About 40% of moderate-to-severe atopic dermatitis cases in children are accompanied by IgE-mediated food allergy, which contributes to significant deterioration in the quality of life of patients [3, 4]. Early onset (less than 3 months of age) and severe course of AD are associated with an increase in the blood level of specific IgE to eggs, milk, and peanuts [5]. Food allergens trigger AD aggravation in 33% of patients with a severe course of AD, 10–20% of patients with moderate AD, and 6% of patients with mild AD [6–8].

The dual-allergen exposure hypothesis suggested by G. Lack et al. (2008) provides a possible explanation for a strong correlation between AD and accompanying food allergy. According to this hypothesis, a sufficient vitamin D level, gut microbiota diversity, and the natural route of food allergen penetration through the gastrointestinal tract induce oral tolerance. Exposure to low doses of food allergens from the environment (on surfaces, hands, and in dust) through the impaired skin barrier, vitamin D deficiency, and decreased gut microbiota diversity lead to the development of sensitization [9].

This review article analyzes in detail the mechanisms of the formation of epicutaneous sensitization according to available modern research data and considers controversial issues that contradict this hypothesis.

DATA SOURCES

The authors analyzed studies on epicutaneous sensitization using the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and UpToDate (https://www.uptodate.com/) databases. The review uses original articles published over the period from 1998 to 2020. Preliminarily, the search in PubMed was conducted using the following key words: epicutaneous sensitization, atopic dermatitis, skin barrier defect, food allergy. The search in UpToDate was performed using the following key words: pathogenesis of food allergy, atopic dermatitis pathogenesis, clinical manifestations and diagnosis. The search for studies corresponding to the listed terms was also carried out among the lists of references and citations in the selected publications. 420 publications from the PubMed database were studied. At the stage of publication selection, articles with the absence of the required data in the abstract text were excluded. A total of 289 publications were analyzed. Subsequently, the analysis of full-text publications was carried out. The criteria for eligibility were originality of the article, the English language, publications in journals included in the international citation system Web of Science (www.webofknowledge.com)/Scopus), compliance of the submitted data with the subject of the article. The exclusion criterion was the absence of the required data in the text of the article. Based on the selection results, this article includes data from 101 sources.

EXPERIMENTAL MODELS OF FOOD SENSITIZATION FORMATION

Experimental data now suggest that development of food allergy is closely related to exposure of an allergen through the skin [10]. First attempts to prove the possibility of epicutaneous sensitization were made in experimental models in mice. In the study, applications of ovalbumin (chicken egg protein) to damaged skin caused an increase in the specific IgE. Consequently, when the allergen was administered orally, the mice developed an anaphylactic reaction with an increase in histamine and histological changes in the intestine and lungs [11].

Later, J. Strid et al. (2004) showed that the immune response caused by epicutaneous exposure to an allergen is directed towards the Th2 pathway. This kind of reaction was obtained when various types of mice were exposed to various antigens. [12–16]. In these studies, microdamage to the skin is a model of skin barrier impairment, which is observed in patients with AD. A series of experimental studies showed that preliminary sensitization of mice using the epicutaneous route of allergen penetration through damaged skin leads to inhibition of oral tolerance induction [17, 18].

ROLE OF SKIN BARRIER DEFECTS

One of the important links in the pathogenesis of AD is impairment of the epithelial barrier, which significantly increases the risk of developing food allergies and other allergic diseases. The barrier function of the skin is provided mainly by the stratum corneum, which consists of corneocytes and extracellular matrix. Corneocytes are held together by tight junctions and corneodesmosomes. Loss of function of corneodesmosin, a gene encoding components of corneodesmosomes, in various congenital defects leads to severe defects in the skin barrier, itching, and atopy [19].

FILAGGRIN DEFECT

Currently, the defect in the *FLG* gene encoding filaggrin occupies a prominent place in impairment of the skin barrier. Filaggrin is a major epidermal protein which is crucial for the structure and function of the stratum corneum, which provides a physical barrier [20]. Mutations in the filaggrin-encoding gene are considered some of the most important risk factors for sensitization and development of a number of allergic clinical phenotypes, most likely due to exposure to allergens through the skin [21]. Data from a systematic review and meta-analysis of 24 studies suggest that the presence of an impairment in the skin barrier is fundamental in the development of allergic diseases. Filaggrin defects increase the risk of developing sensitization, atopic eczema, allergic rhinitis, and bronchial asthma in individuals with eczema [22, 23].

Children with a *FLG* gene mutation were 2.4 times more likely to develop a food allergy confirmed by an oral challenge test. Initially, it was shown that children with *FLG* mutations have higher prevalence of sensitization to peanuts, increasing the risk of developing IgE-mediated allergy by more than 5 times [24].

This was also proven in another study in the UK, which was aimed at investigating the effect of mutations in the *FLG* gene on the risk of developing food allergy to peanuts. The amount of peanut antigen in houses where children of the first year of life lived was measured. To identify sensitization and confirm food allergy, skin prick tests and determination of specific IgE to peanut allergens Ara h 1,2,3 in the blood serum by the ImmunoCAP method were used. Oral peanut

test at the age of 8 and 11 years and genotyping were used for six *FLG* gene mutations. The results of the study indicate a significant increase in the risk of sensitization and peanut allergy in children with the *FLG* mutation compared with children without skin barrier impairments, confirming the hypothesis of transcutaneous sensitization [25].

An association between filaggrin mutation and food allergy, not only to peanuts, but also to eggs and milk, as proven by a provocation test, was shown in the genome-wide association study (GWAS), with a significant association observed even in the absence of eczema [26].

Filaggrin gene mutations increase the chances of developing sensitization not only to food, but also to inhaled allergens. In the UK, a population-based cohort study of 1,051 children was conducted, which showed a significant increase in the risk of sensitization to the major cat allergen Fel d1 among children with filaggrin mutations compared with children without them. It was also noted that the risk of developing sensitization to house dust mite with increasing exposure to Der p1 (a major allergen of house dust mites) was consistently higher among children with filaggrin mutations [27, 28].

Other factors that are crucial in disrupting the skin barrier include changes in the structure of the lipid composition of the intracellular matrix, an imbalance between stratum corneum protease and antiprotease activity, tight junction dysfunction of the stratum corneum, microbial colonization, and release of proinflammatory cytokines.

TRANSEPIDERMAL WATER LOSS

The extracellular matrix of the stratum corneum consists of multiple lamellar membranes enriched with ceramides, cholesterol, and free fatty acids.

The study by C. Cole et al. (2014) demonstrated that changes in the lipid composition of the epidermis cause impairment of the epidermal barrier regardless of the presence or absence of the filaggrin gene mutation [29]. A later published meta-analysis revealed that changes in the lipid layer composition in patients with AD occur both in skin lesions and on visually healthy skin [30]. Lipid barrier impairment entails increased transepidermal water loss (TEWL), which is crucial in the pathogenesis of food allergy in newborns. It was discovered that 75% of children suffering from food allergies had high rates of TEWL in infancy, and even in the absence of atopic dermatitis, the risk of developing food allergies was 3.5 times higher [31].

Further studies confirmed these data; it was found that excessive TEWL in the first week of life is an independent risk factor for the development of AD and is associated with higher allergic sensitization.

TIGHT JUNCTION DYSFUNCTION IN THE STRATUM CORNEUM

Tight junctions are transmembrane protein complexes that provide keratinocyte adhesion, thereby creating a permeability barrier for the intercellular space. They regulate paracellular transport of liquids and solutes. This is important because it determines the nature of ion and protein transport and even penetration of Langerhans or dendritic cells. Tight junctions are located directly under the stratum corneum, forming the so-called second barrier in the epidermis [32].

In patients with AD, a congenital deficiency of transmembrane tight junction proteins is observed, which is especially pronounced in the presence of a filaggrin gene mutation. A. De Benedetto et al. (2011) found a decrease in the expression of claudin-1, -4, -23 in patients with AD with undamaged skin [26]. It is important to note that a decrease in the expression of tight junction components was associated with a significant change in the bioelectric characteristics of the epidermis in AD (not damaged and not exposed to the sun) with noticeably lower transepithelial electrical resistance, higher albumin permeability, and associated selective ionic permeability. This is also shown by earlier studies on mice in which the claudin-1 gene was “turned off”, and in the first 24 hours after birth, TEWL was observed, which led to their death [33].

An inverse correlation was also noted between the expression of epidermal claudin-1 and markers of the Th2 response (eosinophilia, total IgE level). This suggests that the Th2 response may inhibit the expression of the key members of the claudin family (e.g., claudin-1, -4, -23) or the other way round. To investigate whether changes in the claudin-1 gene could be associated with AD and its more severe course, two populations (African Americans and Caucasian Americans) were studied. The strongest association was observed in the African American population, with changes in the claudin-1 gene being associated with earlier onset and a more severe course of AD. Weaker associations were observed among Caucasian Americans. It is interesting to note that some defects in the claudin-1 gene are associated with sensitization to contact allergens in the North European population [34].

PROTEASE AND ANTIPROTEASE ACTIVITY OF THE STRATUM CORNEUM

The skin barrier function can also be impaired in cases of genetic disorders with an increased level of chymotrypsin and trypsin enzymes in the stratum corneum. These enzymes cause premature destruction of corneodesmosomes, which leads to disruption of the skin barrier [36].

The *KLK7* gene encoding chymotrypsin was tested for variations in healthy children and children with AD. Defects in the *KLK7* gene were assessed and their possible association with dysregulation of chymotrypsin in humans, leading to thinning of the skin barrier. The strongest association was observed in the subgroup of patients who did not have elevated IgE levels. This association was not significant in the subgroup of patients with high serum IgE [37].

When endogenous proteases are produced excessively, premature desquamation of the stratum corneum occurs, and a thinned skin barrier is formed. This facilitates penetration of allergens, which can further cause AD or its aggravation. External effects, such as washing with detergents and prolonged use of topical corticosteroids can further increase the production of these enzymes in the stratum corneum and impair the skin barrier function [36]. Normally, the activity of proteases involved in epidermal desquamation is regulated by several protease inhibitors co-expressed to balance the rate of stratum corneum degradation.

Genetic mutations have also been identified in genes encoding elements of inhibitors of these proteases. For example, mutations in the *SPINK5* gene, which encodes serine protease lymphoepithelial Kazal-type 5 inhibitor, have been associated with Netherton syndrome. Patients with this syndrome have severe barrier dysfunction, including increased desquamation and impaired keratinization. Several studies showed a link between a defect in the *SPINK5* gene and AD [38–41]. In addition, damaged skin cells can produce endogenous proteases that further impair the skin barrier. These proteases can be considered as a product of an inflammatory response, and their level is proportional to the severity of AD aggravation. Mast cell chymase is a chymotrypsin-like serine protease that is primarily stored in the secretory granules of mast cells. In one study, mast cell chymase level was significantly increased in AD patients in damaged skin compared with intact skin. However, no significant difference was found in the level of mast cell chymase between intact skin in AD patients and healthy individuals, which suggests that increased mast cell chymase activity may be associated with active dermatitis [42].

There is also evidence that mast cell chymase may be involved in the development of chronic dermatitis by inducing eosinophilic infiltration [43]. Different variations in the chymase-encoding gene have been associated with AD in children, the association being the strongest in individuals with low total serum IgE [44].

The skin barrier can also be damaged by exogenous proteases from house dust mites and Staphylococcus aureus [45]. House dust mites are a source of over 30 different proteins that can induce IgE-mediated responses. Some of these proteins are cysteine and serine proteases. Patch tests have shown that two proteins with proteolytic activity derived from house dust mites, Der p 1 and Der p 2, induce skin irritation or immune activation through direct proteolytic activity [46].

ROLE OF STAPHYLOCOCCUS AUREUS IN THE FORMATION OF EPICUTANEOUS SENSITIZATION

At present, there is a large body of scientific data proving the role of *St. aureus* in the pathogenesis of AD [47]. Epicutaneous sensitization with staphylococcal enterotoxin induces local inflammation corresponding to eczema in mice and subjects with normal and atopic skin [48, 49]. Population-based cohort studies report that colonization of the skin or nasopharynx by *St. aureus* precedes the clinical diagnosis of eczema in infancy. In addition, patients with eczema are more prone to colonization with *St. aureus* than healthy controls, and disease severity is associated with colonization of the affected skin with *St. aureus* [50].

St. aureus can cause significant impairment of the skin barrier and thus contribute to the development of food sensitization through epicutaneous exposure to the allergen. Moreover, *St. aureus* causes skin disruption as a result of exotoxins and protease and lipase production.

Exposure to the peanut antigen through the skin in the presence of *St. aureus* enterotoxin significantly enhanced the CD4 + Th2 response in mice, suggesting that *St. aureus* contributes to the development of food allergies. Exposure to *St. aureus* toxin in mice also led to an increase in Th2-mediated responses and a decrease in the regulatory function of T cells, both of these mechanisms having been described in patients with food allergies [51, 52]. In a retrospective study

by A.L. Jones et al., skin cultures from AD patients aged 0–18 years were analyzed. The data obtained indicate the presence of an association between colonization of the skin by *St. aureus* and food allergy to peanuts, egg white, and cow's milk in patients with AD [53]. Later, in the study by O. Tsilochristou et al. (2019), conducted in the age group of 0–6 years, it was shown that, regardless of the severity of eczema, there was an association with sensitization to chicken eggs and peanuts and a weaker association with cow's milk [55].

Thus, various impairments of the skin barrier, including colonization by *St. aureus* lead to immune dysregulation, ultimately contributing to the development of food allergies through local exposure to the allergen [54].

A question arises, how food allergens penetrate the skin. A number of studies showed the presence of food allergens in house dust, not only in the cooking area, but also in children's beds [56, 57]. For example, in Norway, dust samples from 143 houses were found to have fish allergen in 46%, peanuts in 41%, milk in 39%, and egg allergen in 22% of mattress dust samples [58]. Food allergens can be found in cosmetics used for the basic therapy of atopic dermatitis, resulting in direct contact of food proteins with the affected skin [16, 59]. An analysis of data from the study involving 13,971 preschool children showed a significant association of peanut allergy with skin care products containing peanut butter [60]. Despite the proven role of skin barrier impairment in development of epicutaneous sensitization, it is not the only component in its pathogenesis.

ROLE OF IMMUNE MECHANISMS IN THE DEVELOPMENT OF SENSITIZATION

Epidermal exposure to allergens selectively stimulates the Th2 type reaction, leads to an increase in the thickness of the epidermis, a rise in the level of antigen-specific IgE in the blood serum, and production of cytokines, and may contribute to the development of an allergic reaction upon subsequent exposure to the allergen through the gastrointestinal tract, where mast cells accumulate, as evidenced by an increase in the serum level of mast cell protease-1 (MCP-1) [61–63].

The immune response in food allergy includes two phases (Figure). The first phase begins with absorption of antigens by dendritic cells and their transport to the lymph nodes, where the antigen is presented to naive CD4+ T cells. In the lymph nodes, in the presence of interleukin (IL)-4 and cytokines, T cells differentiate into allergen-specific CD4 + T cells, producing high levels of cytokines (IL-4, IL-13) that, in turn, facilitate the production of B cell isotypes – specific IgE memory cells [64].

Due to the facilitated antigen presentation, a very low concentration of allergen can stimulate the formation of a complex between specific IgE, the allergen, and the low-affinity IgE receptor on the surface of antigen-presenting B cells (CD23+ cells). This complex then further stimulates Th2 cell proliferation, leading to further B cell isotype switching and increased IgE production [65, 66].

As B cells mature, they differentiate into plasma cells and produce large amounts of allergen-specific IgE antibodies (sIgE) that bind to high-affinity FceRI receptors on the surface of mast cells and basophils. During this phase, a memory pool of allergen specific B cells and allergen specific CD4+ Th2 cells is generated. Recently, it has been suggested that a subset of Th2 cells (Th2A cells) play an important role in the immune response to allergy. Congenital group 2 innate lymphoid cells (ILC2), which are found on the surface of the lungs, intestines, and skin, serve as key regulators and effectors of immunity and promote tissue repair. They are also found in human skin lesions in AD and are activated by IL-33. ILC2 secrete proallergic cytokines, including IL-5 and IL-13. IL-5 triggers recruitment of eosinophils. IL-13 promotes recruitment of inflammatory cells, alters skin microbiome, and reduces the epidermal barrier.

The effector phase follows the sensitization phase and is triggered when a person encounters a previously sensitizing allergen. This causes cross-linking of the FceRI-bound receptor with sIgE on sensitized mast cells and basophils, resulting in the release of preformed and *de novo* inflammatory mediators. These processes lead to an immediate phase of an allergic reaction and, subsequently, to a late phase of an allergic reaction through activation of allergen-specific Th2 memory cells [64].

Activated Th2 cells produce, among other cytokines, IL-4, IL-5, IL-13. Recent evidence suggests that IL-13 is a key cytokine that stimulates peripheral inflammation in AD, while IL-4 has a more central effect [13, 67]. The primary importance of IL-4 in the development of both sensitization and IgE-mediated food allergy is confirmed by the absence of IgE production in the presence of anti-IL4 antibodies [69]. Eosinophils and basophils are the predominant IL-4 competent cells that accumulate in the skin in response to transepidermal penetration of food allergens

[70]. Cytokines support allergen-specific IgE levels, eosinophilia, mucus production, and recruitment of inflammatory cells in the inflamed tissues, leading to tissue damage.

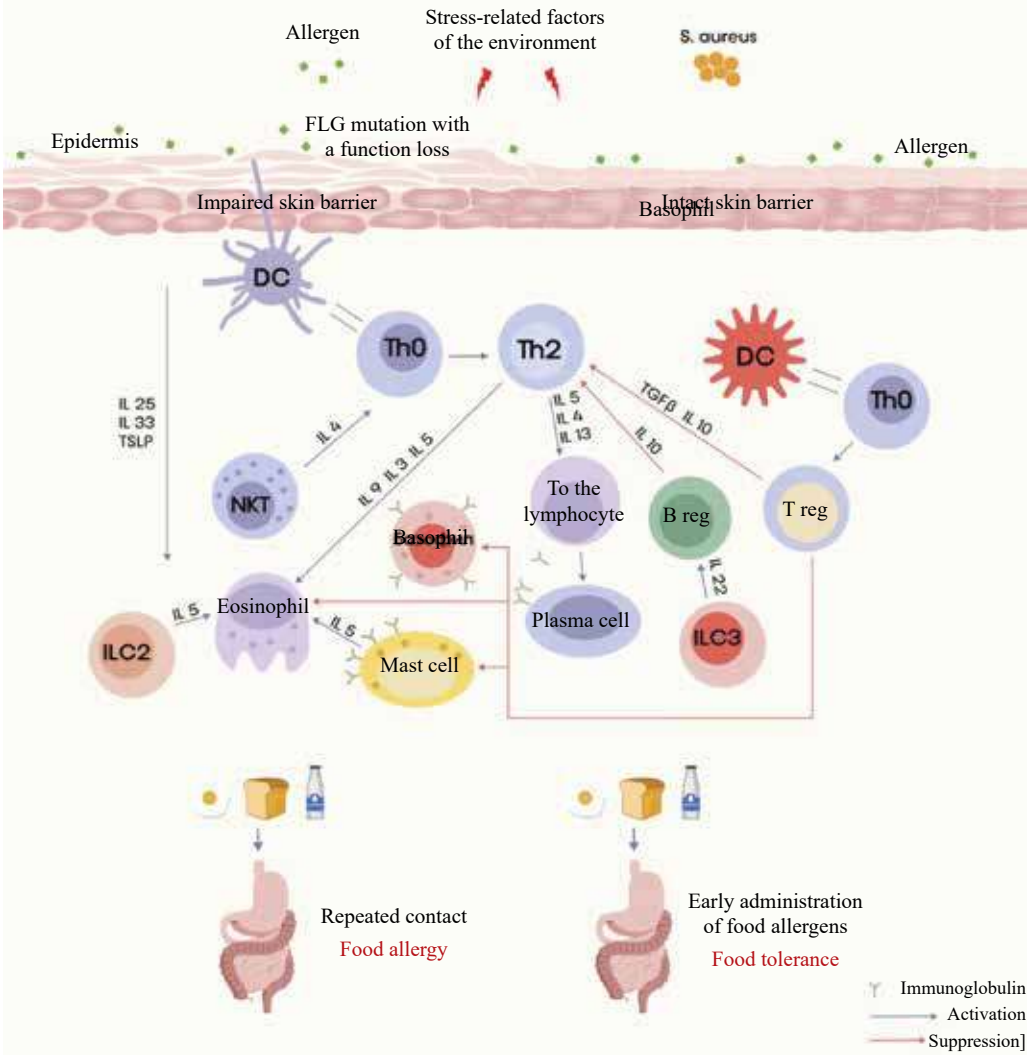

Figure. Immune mechanisms in the development of epicutaneous sensitization: NKT – natural killer cells, B reg – B regulatory cells, ILC2 – congenital group 2 innate lymphoid cells, ILC3 – congenital group 3 innate lymphoid cells

ROLE OF THYMIC STROMAL LYMPHOPOETIN IN THE FORMATION OF EPICUTANEOUS SENSITIZATION

Thymic stromal lymphopoetin (TSLP) is one of the most important cytokines involved in epicutaneous sensitization [68]. This cytokine is elevated in the stratum corneum in patients with AD and correlates with the severity of the disease [71].

TSLP-deficient mice were protected from the development of allergic inflammation of the skin, respiratory tract, and food allergy after exposure to the antigen. These experimental data prove the importance of this cytokine in allergic sensitization [72–75]. The proinflammatory cytokines TNFα and IL-1a, produced in response to skin damage, induce the secretion of TSLP from human keratinocytes.

TSLP expression correlates with maturation of Langerhans cells, regulation of the TSLP receptor on these cells, and their migration to lymph nodes, where they promote the differentiation of naive Th cells into Th2 cells [76]. TSLP induces the migration of Th2 targeted antigen-presenting cells to the mesenteric lymph nodes, thereby promoting the development of allergic reactions in the intestine. These data indicate the association of TSLP with early stages of epicutaneous sensitization [77].

ROLE OF IL-33 IN THE FORMATION OF EPICUTANEOUS SENSITIZATION

Research data also indicate the possible key role of IL-33 in the development of epicutaneous sensitization [45, 78]. IL-33 is a part of the IL-1 cytokine family. It is expressed in epithelial barrier tissues and lymphoid organs and is crucial in the initiation of allergic inflammation after exposure to an allergen [79].

The level of IL-33 was elevated in the affected skin and serum of patients with AD, as well as in experimental models in mice after epicutaneous sensitization with ovalbumin [80, 81]. IL-33 promotes increased secretion of IL-5 and IL-13 by polarized Th2 lymphocytes and is associated with increased serum IgE levels and eosinophilia [82]. A study investigating the role of IL-33 in epicutaneous sensitization in food allergy showed that IL-33 is required to induce IgE-dependent anaphylaxis. IL-33-deficient mice and mice treated with a soluble IL-33 antagonist were protected from oral allergen-induced anaphylaxis [83].

C. Galand et al. (2016) in their work demonstrated that mechanical damage to the skin caused by the removal of the adhesive tape in mice epicutaneously sensitized with ovalbumin induced local and systemic release of IL-33, which led to an increase in IgE-mediated degranulation of mast cells and oral allergen-induced anaphylaxis [84]. Blockade of ST2 (IL-33 receptor) by anti-ST2 monoclonal antibodies led to inhibition of the anaphylactic reaction and suppression of the production of antigen-specific IgE and inflammatory mediators [85]. The existing data suggest that IL-33 plays a key role in epicutaneous sensitization. Neutralization of IL-33 is currently considered a promising strategy for the treatment of food allergy and AD [86, 87]. IL-24 involved in the suppression of filaggrin production in keratinocytes performs an important function in the development of AD [88].

MECHANISM OF FOOD TOLERANCE FORMATION

Several factors, including allergen properties, dose, entry route, genetic factors, and age, contribute to the development of food tolerance or sensitization [89]. In the context of discussing sensitization to food, the entry route of the allergen is the most important. Initial exposure to the food allergen by the extraintestinal route is more likely to lead to sensitization. If the skin barrier is not impaired and the immune system is not primed through the skin, the tolerance mechanisms are triggered [9].

Experimental models show that tolerance is mediated by various mechanisms, such as anergy and deletion of lymphocytes, as well as suppression of sensitization by T regulatory cells [90]. Regulatory T cells are thought to induce tolerance by secreting suppressive cytokines, IL-10, and transforming growth factor (TGF) β (Figure).

The age of exposure is also crucial in the induction of oral allergen tolerance. In the experimental study, feeding newborn mice with albumin led to priming of humoral and cell-mediated responses, while in adults this caused tolerance [91]. Developing tolerance is important in preventing the development of food allergies [92, 93]. Interestingly, countries that have peanut snacks for children have relatively low rates of peanut allergy [94]. It was shown that early introduction of milk, eggs, and peanuts reduces the risk of developing food allergies [95, 96]. Based on the data obtained in 2014, the EAACI consensus was adopted stating that introduction of products during the window of tolerance (the interval between 4–7 months of a child's life) is recommended for all children, regardless of the presence of an atopic predisposition [97].

PREVENTIVE EFFECT OF EMOLLIENTS ON THE FORMATION OF FOOD ALLERGY

According to the available data, a defect in the skin barrier along with immune dysregulation are the leading mechanisms in the formation of epicutaneous sensitization. Various strategies are currently being developed to reduce the risk of formation of AD and food allergy. One of the relevant areas of development is preventive use of emollients in children who have a history of atopy. The idea of using emollients in the context of food sensitization is that, by protecting the skin barrier, they should prevent penetration of the allergen and, as a result, development of sensitization. However, currently, there are many unresolved issues and controversial points regarding the effectiveness of their use.

The study by H. Kenta et al. (2014) showed that the use of emollients in children in the first 32 weeks of life prevented the development of AD in 32% of cases in comparison with the control group [98]. Similar data were also published in 2014, according to which, in children with a high risk of AD, the preventive effect of emollients is independent of the presence of a filaggrin gene defect [99].

At the same time, the study by R.C. Joanne et al. (2020) provided no confirmation of the preventive effect of emollients. The multicenter, randomized study

involved 1,394 children, of whom 693 individuals received emollients (Diprobase cream or Doublebase gel), and 701 children were in the control group. At 2 years of age, eczema was present in 139 (23%) of 598 infants in the emollient group and in 150 (25%) of 612 infants in the control group [100].

Additionally, in the work by E. Dissanayake et al. (2019), which studied the use of emollients in children who were not at high risk of developing AD, no effect from the prophylactic use of emollients was observed [101]. One of the possible reasons for such differences may be the sample of the study population, which was an ordinary-risk group for the development of AD, while in other studies the high-risk group was examined. At the same time, regardless of the obtained effect from the use of emollients to prevent AD, the authors of the works in which the end point of the study was not only AD but also food sensitization agree that emollients do not affect the prevention of food sensitization.

Thus, the aforementioned work by H. Kenta et al. did not find a statistically significant effect on allergic sensitization based on the level of IgE to egg white. However, the level of sensitization was significantly higher in infants with AD [98]. Moreover, no relationship was found between the use of emollients and the development of food allergies; the difference with the control group was only 2% in the work of E. Dissanayake et al. [101]. There are currently insufficient data to draw definitive conclusions for or against this method of preventing food allergy. It should be noted that the effectiveness of the preventive use of emollients must be assessed based on the composition of the specific agent used, therefore further research is required.

CONCLUSION

A large body of data has been accumulated on the possible existence of epicutaneous sensitization, in which priming of immune cells occurs, and, subsequently, food allergy develops. Along with experimental studies confirming the role of epicutaneous sensitization, clinical data were obtained confirming this route of exposure, which opens up ways for possible prevention of food allergies, in particular, early introduction of food allergens, neutralization of IL-33, and preventive use of emollients.

It is assumed that emollients that create a protective film in the case of congenital defects of the skin barrier should prevent penetration of the allergen and, consequently, development of sensitization. However, studies on the preventive effect of emollients have conflicting results: some studies confirm their effectiveness, while others do not. Therefore, additional studies are required on the role, place, and mechanisms of the formation of epicutaneous sensitization in patients with food allergies.

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