REVIEW PAPER

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Oral tolerance induction and food allergy prevention

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ABSTRACT

This review aims to provide an overview of the issue of oral tolerance induction in early childhood and allergy prevention. We discuss changes in epidemiology of allergic diseases that have occurred over the last decades in the context of current knowledge about environmental factors affecting prevalence of these diseases. Also this article presents current data about causes of «hygiene hypothesis» expansion to «microflora hypothesis» as well as an immunological background of this process; describes how immune factors of cord blood and breast milk, maternal and infant's elimination diet, timing a solid food intake impact on immune system development and tolerance induction in early childhood. Current knowledge on issues of oral tolerance induction and allergy should induce update of allergy prevention recommendations in the nearest future.

Keywords: immune factors, cord blood, breast milk, microbiota, elimination diet.

Introduction

Immune tolerance is a state of "unresponsiveness" of the immune system to certain substances or tissue antigens that can potentially induce an immune response. Oral tolerance refers to a specific type of immune tolerance induced by orally ingested antigens such as food [1]. Therefore, it is often called oral tolerance to food antigens. It should be mentioned that gut immune system play a key role in oral tolerance induction. The earliest manifestation of failed oral tolerance induction is sensitization to food allergens. Subsequently, an allergen sensitization profile can expand and progress to clinical manifestation of food allergy and other allergic diseases as well [2]. The exact mechanisms involved in the development of oral tolerance as well as factors influencing this process are being actively studied and discussed, especially in terms of allergy prevention.

Since the 1980s the prevalence of allergic diseases, immune-mediated pathology such as diabetes mellitus type 1 and inflammatory bowel disease have been steadily increasing in developed countries while the incidence of infectious diseases have considerably decreased [3, 4]. WHO has declared an epidemic of noncommunicable diseases due to significant changes in environmental factors as a result of massive urbanization, changes in life style, human nutrition and medicine advancement as well [5, 6]. According to an EAACI prediction more than half of the European population will suffer from allergic diseases by 2025. Most of these diseases already manifest in childhood.

There are two major groups of factors, in particular genetic predisposition and environmental factors, which are crucial for allergic disease development. Obviously, we cannot explain significant changes in the epidemiology of allergies that have occurred over a relatively short period of time only by a genetic predisposition [3]. According to the latest data, about 10% of children who have developed allergic diseases in the first year of life don't have any relatives with allergic diseases and 20–30% of infants with allergy manifestations have first-degree relatives with allergic diseases [7]. The question is why children with negative family history of allergies develop allergic diseases and vice versa why in some cases genetic predisposition to allergy is not accompanied by disease manifestation or why it results in the allergic disease so early?

The role of gut microbiota

For the first time in 1989, D.P. Strachan drew special attention to the fact that allergic diseases were much less common in children who had several siblings and thus were more frequently exposed to infectious antigens. Based on this fact, the "hygiene hypothesis" explaining origin of allergic diseases was formulated by the scientist. Subsequently, this theory was confirmed by other researchers who described the lower incidence of allergic diseases in children living on farms during childhood (so-called "farm effect"), in kids having pets at home etc. [8, 9, 10].

About the same time (1986) T.R. Mosmann with colleagues described two types of T-helper cells (Th1 cells and Th2 cells) secreting different cytokines and therefore initiating various types of inflammatory response. It has been shown that Th2 cells play a key role in the development of allergic sensitization, while viral infection activates the Th1-mediated immune response and inhibits Th2 cytokine activity [11]. This data became the immunological basis of the «hygiene hypothesis». The rapid development of immunology has contributed to modification of an immunological concept of this hypothesis [12]. Of particular importance became the understanding of the gut mucosal immune system's role in immune system development and immune tolerance induction. Evidences provided by researchers over the past 10 years have promoted expansion of the «hygiene hypothesis». The crucial role of intestinal microbiota for immune tolerance induction and to support balance between Th1 and Th2 activities has been shown. This was the reason to rename a previous «hygiene hypothesis» of allergic diseases to «microflora hypothesis» [13, 14].

One of the much discussed issues is the effect of microbiota on immune tolerance induction and its relationship to allergic diseases manifestations, inflammatory bowel diseases, and diabetes mellitus type I [15, 16]. Experimental studies have demonstrated that germ-free mice cannot develop immune tolerance to food allergens [17, 18]. Clinical studies have revealed the link between early life gut dysbiosis and risk of allergic diseases in later life. For instance, children who developed asthma at school age had lower intestinal microbiota diversity during the first month of life [19]. Antibiotic use in early childhood has been shown to be associated with increasing risk of asthma development in early school age as well as inflammatory bowel disease and diabetes mellitus type I [20, 21, 22].

The first 1000 days of life are considered to be a critical period for the development of the individual gut microbiome composition that drives immune system maturation and has an effect on oral tolerance induction [23, 24]. T. Escherich (1857–1911) was a pioneer in studying the intestinal microbiota. His assumption about sterile intestine in utero and colonization by bacteria after birth has been refuted not so long ago [25]. Evidences that exposure to microbes can start in antenatal period have been provided thanks to achievements of molecular biology in the second half of the 20th century as well as recent progress in genome sequencing [26]. Recent studies have shown the presence of microorganisms in amniotic fluid and placenta even in the case of a healthy pregnancy [27]. This data have initiated discussion about changing the paradigm from «sterile womb» to «in utero colonization» hypotheses. [28]. Moreover, for the last decade researchers have been talking about microbial programming of health. For the first time, the hypothesis about fetal origins of many adult diseases, also known as fetal programming, was expressed by Barker D.J. in 1988 [29]. The term microbial programming, as a particular version of fetal pro-

gramming, appeared not so long ago. Despite this fact, there are a lot of studies confirmed this hypotheses [26, 23]. It has been shown that antibiotic use during pregnancy, nutritional habits of a pregnant woman, maternal age and her health condition influence on the maternal microbiome composition and this, in its turn, has an impact on the gut microbiota pattern in the offspring and consequently on the immune system maturation [30, 31]. It is worth mentioning here that human milk is considered to be an important source of initial bacterial colonization of the child's intestine after birth. Recent studies have declared that breast milk can be a source of ¼ commensal bacteria to the infant gut. Daily consumption of 800 ml of breast milk is accompanied by ingestion about 1×10^5–1×10^7 bacteria [32, 33]. It follows from the above that the process of microbial programming begins in antenatal period and continues after birth [34].

Effects of mother's immune factors in the antenatal period

In terms of fetal programming, studying the effect of mother's immune factors on the infant's immune system development during pregnancy has a particular interest. Previously it was believed that the placenta is a kind of barrier that protects fetus from mother's immune system and this way prevents fetus rejection. Recent studies have clearly shown that an impenetrable immunological barrier between mother and fetus is absent [28, 35]. It is already known about transplacental transfer of mother's IgG, cytokines as well as her immune cells (chimerism). These immune factors may interact with the developing fetal immune, that is to say, they might be involved in immune programming [36]. Spectrum of immunologically active components which receive fetus during pregnancy will depend on maternal health, in particular on her allergological status. There are some evidences that confirm the potential significance of events at this period of life for the development of allergies. For instance, researchers have described cases of food allergy development in adults for the first time after cord blood transplantation. This phenomenon was called «transplant-acquired food allergy» [37, 38]. Moreover, it has also been determined lower ratio Treg/Th2 and relatively lower concentration of Th1 associated cytokines (IF-γ) in cord blood of children born to mothers with allergic diseases [39, 40]. As indicated by other studies, children with a relatively lower number of regulatory T-cells as well as reduced ratio of Th1:Th2 in cord blood had a higher risk to develop an atopic dermatitis and to become sensitized to food allergens [41]. A cord blood IgE level as a predictor of atopy and allergic diseases has been studied for a long time; however, findings are conflicting. There are evidences that IgE levels in cord blood differs between mothers with and without atopy and correlates well with IgE levels in maternal blood. However, it is generally recognized that IgE do not cross the placenta barrier. In this regard, scientists have been discussing origin of IgE cord blood suggesting that a possible source of IgE might be its synthesis by the fetus as a manifestation of sensitization to allergens in utero or maternal-fetal transfer of these antibodies during labor. Recently it has become clear that not IgE but maternal cytokines can freely cross placenta barrier. Therefore, using cord blood IgE levels as a predictor of atopy in children is disputable [42, 44, 43]. Anti-inflammatory IL-10, as well as pro-Th2 cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) can easily cross the placenta barrier, thereby taking part in immune programming. Lower levels of Th1-associated chemokines (CXCL10, CXCL11) and higher levels of Th2-associated chemokines (CCL17 and CCL22) in cord blood have been reported to precede allergen sensitization in early childhood [45, 46, 43]. On the other hand, newly published data indicates a protective role of maternal allergen-specific IgG in relation to the development of allergen sensitization in children. There was shown that a higher titer of allergen-specific IgG in the mother's blood in third trimester as well as in cord blood and breast milk are associated with a lower incidence of sensitization to allergens in 5 year-old children [47, 48]. As is already known, food allergen intake by a healthy person mainly induces production of allergen-specific IgG promoting tolerance to these food antigens. The balance between allergen-specific IgE and IgG helps to determine if a person will develop symptoms. Therefore avoidance of allergenic foods during pregnancy should not be recom-

mended for healthy pregnant woman because it not to reduce the risk of sensitization of offspring to these foods and even opposite [49].

Immune factors of breast milk and timing of a solid food introduction

Breast milk is now being acknowledged not only as the best food for a child, but equally important as an exclusive source of immune-related components and biologically active substances. For instance, these components and substances include human milk oligosaccharides, cytokines, immunoglobulins, macrophages, T-lymphocytes (CD4 +, CD8 +, Treg), B-lymphocytes, stem cells, memory immune cells and many others. Immune factors of breast milk do not only «compensate» for immaturity of the infant's immune system, as previously suggested, but factors listed above can easily cross the intestinal barrier due to increased intestinal permeability for macromolecules and immunoglobulins in this period and can directly interact with immune cells in the gut mucosa. It has been shown that immunologic factors in human milk are able to train, modulate and promote the development of an infant's immune system as well as impact the intestinal colonization. It means immunologically active components in human milk can drive infant immune system maturation and affect oral tolerance induction [50, 51]. For example, predominant cytokines of breast milk such as transforming growth factor-beta (TGF-β) and IL-10 are involved in the induction of immune tolerance to food antigens as well as gut microbiota antigens. These cytokines are able to downregulate inflammatory response, are involved in switching from IgM to IgA in B lymphocytes, and suppress immunoglobulin E production; it is therefore expected to affect an oral tolerance induction [52, 53]. That is why a possible role of these breast milk cytokines in prevention or at least suppression of the onset of allergic diseases has been studying over recent years. According to some studies, the predominance of commensal microorganism in the mother's intestine result in a higher level of TGF-β and IL-10 in breast milk, and this in turn is associated with a lower risk of developing allergies in children. The longer TGF-β concentration in milk remains high, the more marked its protective effect against eczema in infants. Therefore, identifying factors that influence the level of TGF-β in breast milk could be a way to prevent food allergy [54, 53]. As it is well known, IL-4 and IL-5 are associated with the development of allergic inflammation; however, effect of these breast milk cytokines on oral tolerance induction is ambiguous [32, 55, 56]. Breast milk contains a wide range of cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-25, IFN-γ, TNFα, TSLP, and TGFβ etc.) but role of each one separately as well as its combinations in the tolerance induction and the infant immune system development are not completely understood and further studies will need to assess biological activity of cytokines taking into account its concentrations.

Furthermore there is conflicting data on the protective role of breastfeeding in relation to allergic sensitization and allergic diseases [57, 58, 59]. For instance, there are some studies that have demonstrated non-permanent or weak relationship between breastfeeding and risk reduction of allergy development, and in several cases the absence of such a link have even been declared [60, 61]. Scientists suggest that conflicting conclusions on this issue might have arisen because of different design of studies, in particular not the same duration of breastfeeding and diagnostic criteria for allergic diseases. However, according to results of current studies the composition of breast milk is considered to be the most important thing what was not taken into consideration in previous studies [62, 63]. It has shown, the human milk composition changes depending on duration of lactation (colostrum, transitional milk, mature milk), woman's health, maternal lifestyle and dietary habits, antibiotics use, and even geographic area of residence, socioeconomic factors [64, 65, 66]. Nevertheless, it is generally accepted, that immune-related components and biologically active substances of human breast milk influence the infant immune system development and, thus breastfeeding is capable of affecting a child's health in a long-term perspective. Researchers agreed that further studies should be provided to find out the relationship between the immune profile of breast milk and the risk of allergic diseases in children.

In addition to cytokines mentioned above, colostrum and mature milk are rich sources of immunoglobulins. The major immunoglobulin in

human milk is sIgA, concentrations of IgM and IgG are considerably lower. IgA is synthesized by B lymphocytes which migrate from the maternal intestinal *Lamina propria* to the mammary glands, known as «entero-mammary link». Antibodies specificity in breast milk reflects a range of antigen exposure in woman's intestine, therefore maternal elimination diet during lactation might influence a concentration of breast milk sIgA which specific to eliminated proteins [67]. This data have been confirmed by the recent study. It showed that mothers on elimination diet had lower concentration of cow's milk-specific IgA in human milk and it was associated with the development of cow's milk allergy in infants [68]. Once again it highlights the maternal elimination diet during lactation should not be recommended as a strategy for preventing child allergy.

Recommendations for infants to avoid allergenic foods to prevent allergic diseases were a mainstream in late 20th century. Recently scientists have been discussing «paradigm shift from allergen avoidance to tolerance induction by intake» [70, 69]. It was determined that the best timing of a solid food introduction is the period from 4 to 6 months. This period is already well known as a window of opportunity for tolerance induction to food allergens. Early introduction of food antigens may induce food tolerance faster than sensitization, while the later introduction of potentially allergenic foods may trigger an allergic response [70, 71]. Accordingly, in terms of tolerance induction the current data no longer supports delaying the introduction of potentially allergenic foods in infant's diet as well.

Conclusions

Thus, our knowledge about the process of oral tolerance and allergy development is constantly increasing. This new insight has brought new perspectives for allergy prevention. In terms of this issue specialists are focusing on induction of oral tolerance in early childhood and environmental controls including life style change. Obviously, clinical practice recommendations on allergy prevention for both high risk children and risk-free children should be revised taking into account newly available data, though further studies might be required.

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