

Disease outcomes as a consequence of environmental influences on the development of the immune system

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Purpose of review

To review recent studies on disease outcomes as a consequence of environmental influences on the developing immune system early in life.

Recent findings

The increasing incidence of 'immunologically mediated disease of affluence', such as allergies, type I diabetes and inflammatory bowel disease (IBD), suggests that they are consequences of common environmental factors. No such factors have been identified, however, and prospective studies fail to support commonly given advice. Interest has, therefore, switched towards factors that could induce and maintain tolerance to allergens and autoantigens. A unifying link between Th1-dependent autoimmune disease and Th2-linked atopic allergy would be a disturbed immune regulation involving T regulatory cells. Microbial colonization of the gastrointestinal tract, linked with lifestyle, may be an important determinant. Several prospective, controlled studies, in which different strains of *Lactobacillus* were given to pregnant mothers and then to their newborn babies for 6–12 months, have shown a modest reduction of immunoglobulin E (IgE)-mediated eczema in infants.

Summary

Currently, there is poor support for giving any particular allergy-preventive advice. Novel potential strategies to enhance immune regulation and tolerance induction include modulation of gut microbiota, for example, by probiotics and prebiotics. Although the results are somewhat encouraging, they are insufficient to base general recommendations on, however.

Keywords

allergy, autoimmune disease, environment, gut microbiota, immune regulation

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Introduction

The prevalence of allergies, diabetes, inflammatory bowel disease and other 'immunologically mediated diseases of affluence' has increased progressively, particularly over the last 50 years. The similarities in the epidemiology strongly suggest a shared environmental influence on the development of immunological mechanisms governing host responses to allergens and autoantigens. The increasing incidence of these diseases is obviously to be found in environmental changes, but so far, no major risk factors have been identified. This has prompted an interest in possible protective factors associated with a traditional lifestyle which have been lost in recent decades. As we are beginning to appreciate the key role of the gut microbiota in immune regulation, there has been an increasing interest to understand, and ultimately to manipulate, our physiological interactions with commensal microbiota.

Immunological background

Cross-sectional and prospective studies indicate that in atopic children, consolidation of Th2-polarized immunity against inhalant allergens is initiated in early infancy [1,2] and may be completed by the end of the preschool years in children who do not develop clinically manifest allergy [2], or even earlier [1]. In contrast, low-level Th1 responses are established in infants who develop allergic manifestations. Prospective studies from Estonia, with a low prevalence, and Sweden, with a high prevalence of allergy, indicate that the regulatory mechanisms are established more rapidly in Estonia [1]. It is possible that a traditional lifestyle is associated with an early induction of a general regulation of T-cell immunity. This notion is supported by the close correlation globally between the prevalence of wheezing and type I diabetes [3]. A unifying link between the increase in both Th1-dependent autoimmune disease and Th2-linked atopic

allergy would be a disturbed immune regulation involving T regulatory cells, rather than merely either Th1 or Th2 immunity.

Interaction with the normal microbial flora of the gastrointestinal tract is the principal environmental signal for postnatal maturation of T-cell function (in particular, the Th1 component) [4,5]. Recognition of these signals is mediated by a series of TOLL-like receptors expressed on cells of the innate immune system and other receptors such as CD14 and it is noteworthy that a polymorphism in the CD14 gene has been associated with high immunoglobulin E (IgE) levels [6].

Microbial colonization of the gastrointestinal tract, linked with lifestyle and/or geographic factors, may be an important determinant of the heterogeneity in the prevalence of the disease throughout the world [4]. These suggestions are supported by observations that germ-free mice do not develop tolerance in the absence of a gut flora [7,8] and by the demonstration of differences in the composition of the gut flora between infants living in countries with a high prevalence and those living in countries with a low prevalence of allergy and between healthy and allergic infants (summarized in [4]).

Clinical aspects

Numerous observational, mostly retrospective, studies over the past 30 years have identified a host of environmental factors encountered early in life that allegedly affect the risk for the development of allergic disease. At the same time, there are numerous equally good studies that have not confirmed the findings. It would be inconceivable to introduce a new treatment of a disease with so little evidence. Although advice that hopefully would reduce the risk of allergy is given with good intention, it may cause harm by interfering with and putting an extra burden on family life, sometimes having moralistic overtones, putting blame on the family and causing guilt feelings and disappointment if it is not effective. Well conducted studies of diet modulation during pregnancy (with the possible exception for probiotics discussed below) demonstrate that little efficacy and potential nutritional hazards, as summarized in a meta-analysis, are therefore important [9].

Studies investigating the relationship between early childhood infection and atopy risk have been inconsistent or difficult to interpret. A large Danish national cohort study [10] including more than 24 000 mother-child pairs found that early infections do not protect from atopic dermatitis. However, they observed that other environmental factors, sometimes taken for indirect markers of microbial exposure (such as early daycare attendance, having three or more siblings, farm residence

and pet keeping) were all protective. It is possible that these protective factors are due to other than microbial exposure. For example, the inverse relationship between number of older siblings and allergy risk may be due to altered maternal immunity as a consequence of repeated pregnancies and exposure to animals could possibly be explained by high zone tolerance induction.

Although sensitization is a strong risk factor for persistent asthma, wheeze and bronchial hyperactivity, the relationship between early allergen exposure and the development of clinical symptoms has not been confirmed. The hypothesis that allergen avoidance early in life would prevent asthma is based on two independent observations that exposure to high levels of inhaled allergen is associated with increased likelihood of sensitization and that asthmatic children were often sensitized in early childhood. No studies have confirmed that the two observations are related to each other, however. On the contrary, it was shown in 1999 [11] and in several subsequent studies [12,13] that early exposure to cats and other pets is associated with less respiratory allergy, including cat allergy, later in life. A recent clinical study [14] may explain the seemingly conflicting data between cat exposure, early sensitization and later allergy. This study showed that pet exposure in infancy was indeed associated with early transient sensitization, but also with tolerance induction, and thus inversely related to sensitization at 6 years of age.

Infant feeding

There is consensus that breastfeeding has multiple health benefits and should be encouraged. This is particularly true in developing countries, where the protection against infections may be a matter of life or death (reviewed in [15,16]). In contrast, the possible protective role against allergies has been a matter of considerable controversy. Recent careful analyses clearly indicate that breastfeeding at most has a minor impact on the development of allergic diseases, whereas there is some reduction in the incidence of wheezing triggered by infections. Even those effects are of limited clinical significance and do not motivate any particular advice to breastfeed.

Currently, many parents are advised to delay the introduction of other foods than breast milk until after the age of 6 months. There are two reasons for these recommendations, which are endorsed by the WHO: breastfeeding should not be disturbed, which is very important in developing countries, and early introduction of food antigens are thought to cause allergy. The scientific support for the latter assumption is poor.

It should be noted that exclusive breastfeeding is a novel practice. Traditionally, various foods have always

been given to breastfeeding infants in all human societies. Indeed, two prospective German studies strongly suggest that late introduction of solid foods do not prevent eczema. In the GINI study [17], 4700 children were followed from birth annually up to the age of 4 years. There was no association between time of introduction of solids and eczema. In the LISA study [18^{••}], over 2000 children were followed until 6 years of age without any evidence supporting a delayed introduction of solids beyond 4 months for the prevention of asthma, allergic rhinitis or allergen sensitization, whereas a minor effect on eczema could not be excluded.

It is well established that human milk often contains food antigens that may induce IgE antibody formation. The immunologic consequences of introducing foreign antigens while the infant is still breastfeeding are not fully known. As indicated by studies of immunity to infectious agents, it is possible that it represents a mechanism by which immune responses are modulated. In the early 1990s, there was a pronounced increase in the incidence of celiac disease among Swedish infants [19]. Prior to the increase in celiac disease, gluten was gradually introduced while the baby was still breastfed. Then, gluten was avoided for the first 6 months and then more or less abruptly introduced in large amounts. When the national recommendations were changed back to gradual introduction of gluten while the babies were still partly breastfed, the incidence of celiac disease dropped rapidly.

Maternal dietary antioxidant intakes (vitamin E) have been associated with neonatal immune responses to allergens [20], justifying further studies of the effects of antioxidants on early immune function. A prospective observational study [21[•]] suggested that a 'Mediterranean diet' during pregnancy was associated with less persistent wheeze, atopic wheeze and atopy at the age of 6 years. This diet is characterized by high intake of fruits and vegetables, bread and cereals legumes and nuts and low-to-moderate amounts of dairy products and eggs and only small amounts of red meat. This study is of particular interest, as a holistic approach to diet was employed, rather than looking on particular single food items. It is possible that any effects of this diet are indirect and mediated by stimulating a particular gut microbiota, rather than being an effect of an effect caused by a particular food component.

Microbial stimulation

Intestinal microbiota is arguably the most abundant source of early immune stimulation and contributes significantly to 'microbial burden' in early life. A number of studies have suggested differences in colonization pat-

terns of infants who go on to develop allergy [22]. These differences were already apparent at 1 week of age, suggesting that early colonization can influence subsequent patterns of immune development.

Numerous epidemiological studies have suggested that various components in the diet may protect against allergy or are associated with disease. The data are conflicting and not always reproducible. It is possible that the observed relationships between diet and allergy are indirect and secondary to an effect of diet on the composition of the gut microbiota. If this is the case, then the effects would be expected to vary depending on the composition of microbiota in a certain environment.

It is intriguing that microbial stimulation, in particular via the gastrointestinal tract, is implicated as an etiologic factor in respiratory allergic diseases. This suggests that microbial stimuli from the gut exert effects beyond the mucosal tissue microenvironments adjacent to sites of exposure and presumably can influence systemic precursor compartments such as bone marrow and thymus. A full understanding of the underlying mechanisms may open new venues for the prevention by modification of the gut microflora, not only of local disease manifestations, such as food allergy, but also conceivably on diseases with manifestations at distant sites, such as diabetes and respiratory allergies.

Probiotics

Probiotics are defined as live microorganisms that have beneficial effects on health beyond their nutritional value. Prebiotics are nondigestible, but fermentable oligosaccharides (food starches) that specifically stimulate the growth of *Bifidobacteria* and *Lactobacilli* species. It was logical to explore the benefits of probiotics in infancy, that is, at an age when immune responses are still developing, and there are now several recent published studies that address the role of probiotics and prebiotics in allergy treatment. The studies were critically analyzed in an excellent meta-analysis of 12 randomized, controlled trials of live microorganisms for the treatment of eczema [23^{••}]. Although there was significant heterogeneity between the studies, the conclusion was that probiotics are not an effective treatment for eczema.

The results are more encouraging for prevention rather than treatment of eczema. Over the past 2 years, several controlled studies have been published in which probiotic bacteria were given to infants with a family history of allergy. In most of the studies, the study products were also given to their mothers during the last month of pregnancy. Data from six double-blind, randomized prevention studies of childhood atopic dermatitis by the administration of strains of *Lactobacillus* were

summarized in a meta-analysis [24]. The conclusion was that prevention corresponded with summary effect size of 0.69 [95% confidence interval (CI) 0.57–0.83].

Since then, two controlled studies have assessed the potential eczema-preventive effects of probiotics. In a German study, there was no eczema-preventive effect of *Lactobacillus* GG [25[•]], despite an almost identical design to that employed in a previous Finnish study reporting an impressive 50% reduction [26].

In a study from New Zealand, comparing two probiotic strains with placebo, it was reported that supplementation with a strain of *L. rhamnosus* from 35 weeks of gestation and then to the baby daily from birth until the age of 2 years reduced the risk of eczema as compared with placebo [27[•]]. In that study, a strain of *Bifidobacterium lactis* Bb12 had no effect as compared with placebo. Similarly, the strain of *Bifidobacterium Bb12* did not accelerate tolerance to cow's milk protein in infants with allergy to cow's milk [28].

As it appears increasingly unlikely that supplementation with a single probiotic strain will be sufficient to overcome the high environmental pressure to develop allergic disease, there has been an interest in dietary substrates that could potentially have a more global effect on gut flora, namely prebiotics. A prebiotic effect could conceivably explain some of the protective effects of grains and cereals that have been seen in epidemiologic studies [29]. At this stage, however, there is still very little data to directly confirm the immunological or therapeutic effects of prebiotic supplements, although one recent study [30] has reported encouraging results.

Conclusion

It is obvious that the increasing incidence and prevalence in affluent societies of allergies and other immunologically mediated diseases, such as diabetes and IBD, particularly over the past 50 years, are consequences of environmental changes. For many years, various allergy-preventive measures have been recommended to parents of infants, particularly to those with a family history of allergy, so-called 'high-risk' babies. The advice has not been based on evidence-based medicine, but rather on assumptions and observed relationships in epidemiological studies. Today, no particular advice for allergy prevention can be given, with the exception for less eczema in infants receiving a hydrolyzed infant formula, rather than regular cow's milk based products.

Over the past few years, the studies of possible environmental factors causing this increase have switched from a search for risk factors that would trigger disease to efforts

to identify protective factors in the environment that have diminished or been lost in modern societies. Rather, current research is devoted to identifying protective factors in infancy that would enhance tolerance induction and immune regulation. The gut microbiota is an obvious candidate for such studies. So far, prospective studies with probiotic bacteria have shown limited success and only resulted in modest reduction in the incidence of eczema in infancy. It is conceivable that it is too simplistic to believe that merely introducing one or a few strains of bacteria into the very complex gut microbiota, comprising perhaps 1000 species and numerous strains with each species.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This is a well designed and carefully conducted large study showing that routinely given advice in allergy prevention, such as late introduction of solid foods, is not worthwhile. The study underlines the importance of evidence-based medicine not only for treatment of diseases, but also with regard to advice given for health promotion.

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This study with a negative outcome underlines the importance of confirming previously reported findings by an independent research group. The astounding efficacy of *Lactobacilli* in the prevention of eczema could not be confirmed despite carefully reproducing the design of the original study.

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