Promising candidates for allergy prevention

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Recent advances in understanding environmental risk factors for allergic diseases in children have led to renewed efforts aimed at prevention. Factors that modify the probability of developing allergies include prenatal exposures, mode of delivery, diet, patterns of medication use, and exposure to pets and farm animals. Recent advances in microbial detection techniques demonstrate that exposure to diverse microbial communities in early life is associated with a reduction in allergic disease. In fact, microbes and their metabolic products might be essential for normal immune development. Identification of these risk factors has provided new targets for prevention of allergic diseases, and possibilities of altering microbial exposure and colonization to reduce the incidence of allergies is a promising approach. This review examines the rationale, feasibility, and potential effect for the prevention of childhood allergic diseases and explores possible strategies for enhancing exposure to beneficial microbes. (J Allergy Clin Immunol 2015;136:23-8.)

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More and more children have allergic diseases and other inflammatory disorders.[1,2] These are lifetime diseases that can be severe and progressive and are associated with significant morbidity and some mortality. These disturbing trends, together with skyrocketing health care costs, have redoubled national and international efforts to prevent allergic diseases in childhood. The National Institutes of Health has sponsored conferences on prevention[3] and birth cohort studies[4] to review what is known about the origins of allergic diseases and to develop an evidence-based map for research priorities. Furthermore, the US Centers for Disease Control and Prevention has developed an initiative entitled "National prevention strategy: America's plan for better health and wellness," which emphasizes 4 elements: (1) building healthy and safe community environments, (2) expanding quality preventive services in both clinical and community settings, (3) empowering people to make healthy choices, and (4) eliminating health disparities.[5] There are corresponding multifaceted strategies for preventing cardiovascular disease, obesity, and chronic lung disease, but interventions to prevent allergic diseases are noticeably absent. New developments in understanding disease pathogenesis and the early-life origins of allergic disease raise hope that prevention of allergic disease is achievable. This review will evaluate promising candidates for primary prevention of allergic disease. Given the recent advances in understating how the microbiome affects immune development and the risk of allergy, potential strategies for altering microbial exposures in early life to prevent childhood allergy are explored in detail.

ASSESSMENT OF RISK FACTORS: WHAT ARE THE OPPORTUNITIES FOR INTERVENTION?

Genetics, environmental exposures, age of exposure, and lifestyle and child-rearing practices all contribute to the risk of allergic diseases in childhood. Genetic variations can modify the risk of allergy by altering the expression or development of immunoregulatory pathways that promote type 2 immunity (receptor for IL-33 *[IL1RL1]* and signal transducer and activator of transcription 6 *[STAT6]*), by regulating immune tolerance (forkhead box protein 3 *[FOXP3]*), or by affecting epithelial integrity and permeability (filaggrin *[FLG]*).[6-8] Furthermore, genetic studies have implicated additional variants in genetic regions (eg, loci in 11q13.5 and 5q22.1) that promote allergic sensitization through unknown mechanisms.[7,9] Thus genetic studies have affirmed longstanding paradigms and also have prompted investigations into novel mechanisms of allergy pathogenesis.

There is convincing evidence that environmental exposures markedly influence the risk of allergic diseases. In Western Europe growing up on a dairy farm reduces the risk of allergic diseases by up to half compared with that seen in nonfarm families.[10] Moreover, Amish children in Indiana have very low rates of allergic sensitization (7%), allergic rhinitis (0.6%), and asthma (5.2%).[11] In addition, the prevalence of allergy can be quite different among populations of similar heritage with different lifestyles. For example, schoolchildren growing up in Russian Karelia (2%) versus Finnish Karelia (27%) have dramatically lower rates of birch pollen allergy (2% vs 27%).[12] Effects of environmental exposures can be genotype dependent. For example, the CD14 genotype can determine the effects of exposures to diverse stimuli, including endotoxin, farm milk, and household dogs, on outcomes such as allergic sensitization, atopic dermatitis, and total serum IgE levels.[13-15] Collectively, this information provides evidence that environmental factors contribute to the incidence of allergic diseases in children.

Epidemiologic and birth cohort studies have identified a lengthy list of specific environmental risk factors for allergic diseases in childhood. Examples of prenatal factors associated

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with childhood allergic diseases include maternal diet and use of antibiotics.[16] Mode of delivery can influence allergy; children delivered by means of cesarean section are at increased risk.[17] Postnatal dietary factors that can affect the risk of allergic diseases include breast-feeding, nutrient content (eg, folate, vitamin D, and n-3 polyunsaturated fatty acids), age of introduction of specific foods (eg, peanut), and consumption of foods containing microbes (eg, raw farm milk).[10,18,19] Relationships between diet and allergic diseases can be complex. In the National Health and Nutrition Examination Survey population, folate levels were inversely related to risk of atopy and serum IgE levels in both children and adults,[20] although in other studies prenatal folate intake was associated with childhood asthma,[21] and early-life serum folate levels were positively associated with risk of sensitization.[22] Allergen avoidance to prevent allergies has been extensively studied, and multifaceted interventions that included dust mite avoidance have demonstrated reduced incidence of allergies, asthma, or both.[23] Several recent studies have fueled a change in prevailing opinions, and the value of allergen avoidance in early life, which was once a cornerstone of preventive recommendations, is now questionable.[24] For example, an interventional study of high-risk infants was successful in reducing exposure to dust mite allergens in the home, but rates of sensitization to dust mite or aeroallergens in general were increased, rather than reduced, at age 3 years.[25] Treatment of infants with medications, such as antibiotics, acetaminophen, and antihistamines, are associated with increased risk of allergic diseases, although whether these effects are causal or confounded by association with underlying illnesses is difficult to determine.[26]

Finally, there is intense interest in how early-life exposures to microbes affect the development of tolerance mechanisms and allergic sensitization. As mentioned previously, growing up in environments with rich microbial exposures is associated with lower risks of allergic disease. Within the farming environment, contact with stables and consumption of farm milk are associated with favorable clinical outcomes. Recently, there are data to indicate that diverse microbial exposures[27,28] and gastrointestinal colonization in early life are associated with a reduced risk of allergic disease.

WHEN TO INTERVENE?

The influence of environmental and lifestyle factors can begin in very early life and even before birth. For example, exposure to environmental tobacco smoke might have the greatest effect on incident asthma when exposure occurs during the prenatal period.[29] This conclusion is also supported by observations within immigrant populations in Western countries. For example, immigrants have lower rates of allergy and asthma in the United States, and rates of allergy increase together with the length of time that a child has resided in the United States.[30,31] These findings indicate that exposures in the first few years of life are critically important in determining the risk of allergic diseases.

Immune mechanisms in allergy

Recent advances help to explain how environmental factors can influence the process of allergic sensitization in childhood, as reviewed by Holt.[32] Historically, identification of T_H1 and T_H2 cells 30 years ago represented a major advance,[33] and soon afterward, allergy and asthma were found to have skewed T_H cell responses characterized by overproduction of type 2 cytokines (eg, IL-4 and IL-13). More recent discoveries have shed light on how environmental processes influence patterns of T-cell differentiation and allergy. For example, epithelial cells are now recognized as important links in the chain of events leading to allergic sensitization.[34] Reduced epithelial barrier function can promote greater penetration of allergens into the subepithelial layers, which are involved in antigen recognition mechanisms.[34] In addition, epithelial damage or stimulation by proteases induces the release of alarmins (eg, thymic stromal lymphopoietin and IL-33). These cytokines in turn act on antigen-presenting cells and innate and adaptive lymphoid cells to promote T_H2 differentiation and allergic sensitization.[35,36]

Some allergens can influence local immune responses through their functional properties or by means of molecular mimicry to promote sensitization. The major dust mite allergen Der p 2 has structural homology with an LPS-binding protein and can activate Toll-like receptor 4, which might serve as an adjuvant to sensitization.[37] Moreover, some allergens are proteases and can activate allergic effector cells and degrade epithelial barrier function.[38-40]

Microbes play an essential role in directing the development and function of the immune system at mucosal surfaces, such as the gastrointestinal tract.[41] These microbes stimulate immune development through effects on epithelial cells and antigen-presenting cells that ultimately modulate T-cell differentiation, including stimulation of regulatory T-cell development.[41,42] Accordingly, mice raised in germ-free environments have disordered immune development that predisposes toward allergic and inflammatory diseases, and repopulation of the gut with specific microbes affects immune development. For example, segmented filamentous bacteria can promote development of IL-17 responses, and bacteria that produce short-chain fatty acid metabolites promote differentiation of regulatory T cells.[42,43] Microbes can exert effects through several mechanisms, including modulation of immune responses and inhibition of growth of pathogenic bacteria.[44] Some microbes produce metabolites (eg, short-chain fatty acids, α-galactosylceramide, and tryptophan metabolites) that influence immune development.[45] The strong influence of gastrointestinal flora on the development of systemic immune responses might be due to the large surface area of the gastrointestinal tract, heavy bacterial colonization, and the large amount of both lymphoid and myeloid cells and tissues in proximity to the intestinal mucosa. Less is known about how microbes on the skin and respiratory tract affect local immunity, but it is clear that commensal bacteria on the skin can modify local immune responses independent of effects of gastrointestinal microbes.[46] It is likely that microbes in the respiratory tract have similar functions.[47]

The importance of understanding immune development in healthy children

As discussed above, allergic sensitization represents a breakdown of tolerance and the development of immune responses that are biased toward type 2 cytokine responses and overproduction of IgE. This implies that prevention of allergy could be accomplished by fostering the development of tolerance mechanisms and by promoting the development of balanced immune responsiveness. Conceptually, this sounds straightforward; however, interventions in early childhood that affect immune development could have unintended consequences.