Early life origins of asthma

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Introduction

Although the first symptoms of asthma can occur at any age, recurrent episodes of wheezing and airway obstruction manifest before the age of 6 years in most patients. This suggests that asthma, at any age, is likely to originate in childhood or earlier; therefore, observations in children and models of early life or infant airway injury and repair will provide important clues to the inception and pathogenesis of this disorder. Recent studies have demonstrated that airway inflammation is a principal feature and factor in the pathophysiology of asthma (see articles by Elias et al., Ray and Cohn, and Lukacs et al. as this Perspectives series continues in the next issue). They have also demonstrated that this response is multifactorial in both origin and nature, because of the involvement of numerous resident and recruited inflammatory cells. Thus, the factors that induce and eventually regulate airway inflammation must be considered in our efforts to define the developmental origins of the asthmatic diathesis.

Inflammation in asthma. Although the number of studies of asthma in children are limited, evidence exists that airway inflammation in childhood asthma parallels that found in adults. Bronchoalveolar lavage fluid from children with atopic asthma is increased in mast cells, eosinophils, and eosinophil cationic protein (1). Thus, eosinophils and mast cells appear to be an early component of inflammation in asthmatic children, and must be considered important in the origins of this disease. The contribution of T cells to asthma in children — and, hence, to the onset of asthma — is less clearly defined. An increased frequency of IL-5-producing cells has been found in asthmatic children compared with allergic nonasthmatic children (2). In contrast, the frequency of IL-4-producing cells was increased in both allergic nonasthmatic and allergic asthmatic subjects. In addition, a higher percentage of PBMCs expressing mRNA for IL-2, IL-4, IL-5, and GM-CSF (but not IFN-γ) has been detected (3). Of these peripheral blood markers, the percentage of cells expressing IL-5 correlated best with disease severity. From these early studies, it is evident that IL-5, with its link to eosinophil inflammatory function, and IL-4, with its IgE regulatory capacity, are important lymphocyte-associated cytokines to evaluate as we consider the influence of genetic and environmental factors on the origins of asthma. These observations not only indicate that markers of airway inflammation and mediators that regulate these processes are present in children and appear early in the course of asthma, but they also argue strongly that insight into the origins of asthma mandates an understanding of the pathogenesis of this early life inflammatory response and the effects that recognized asthma risk factors have on its character and natural history.

Genetics. It is believed that the expression of the asthmatic phenotype is dependent upon 2 major factors: a genetic predisposition and environmental interactions (Figure 1). It is the combination of these influences that ultimately determines whether asthma develops and at what time these processes manifest. Therefore, in considering the origins of asthma, the contribution and interaction of both factors is necessary and is the focus of our discussion.

The study of certain genes and their specific affects on asthma is rapidly emerging with the availability of new technologies (4). The pattern of inheritance does not, however, follow Mendelian concepts usually associated with single-gene diseases. Rather, the pattern of inheritance is that of a complex polygenic disorder. Thus, there are likely to be a number of genes that actually predispose individuals to develop asthma. For example, genes whose expression can be linked to airway hyperresponsiveness, IgE production, and cytokine production have been identified. However, a direct link between the expression of these various genetic-regulated processes and the eventual development of asthma has yet to be fully established.

In the search for gene linkages to asthma, 2 features emerge as important, or essential, to its pathogenesis: a predisposition for allergen-specific IgE production, and a capacity to develop acute and chronic allergic inflammation involving mast cells, basophils, eosinophils, and allergen-specific T cells. Asthma-associated genes that regulate these processes can contribute to the development of allergic inflammation, bronchial hyperresponsiveness, and eventual airflow obstruction. Many of the genes for cytokines and receptors that regulate allergic inflammation are clustered on a short segment of chromosome 5q, and linkage of total serum IgE levels to these genes has also been demonstrated in some kindreds (5). Included in the 5q23–31 region are a number of molecules that are likely relevant to the pathogenesis of asthma and the control of IgE synthesis: genes encoding for IL-3, -4, -5, -9, -12, and -13, along with the glucocorticoid and the β2-adrenergic receptor (6, 7). Thus, the 5q region has several candidate genes that may interact and become determinants in the origins of asthma.

IgE sensitivity to house dust mite, cat, cockroach, and Alternaria is environmental risk factors for asthma. Therefore, the identification of those genes responsible for IgE responses to these specific allergens becomes
The development of allergy, or allergic sensitization, and asthma is determined by genetic and environmental factors. Genetic factors include cytokine dysregulation with a tendency toward Th2 responses, or a deficiency of Th1 activity, either of which would promote allergy sensitization. Environmental factors include infections, allergen exposure, and pollutants. Furthermore, the possibility that these interactions will lead to allergy and asthma is dependent upon the age at which these interactions occur.

highly relevant. The human MHC includes genes that code for HLA class I molecules, which are involved in the recognition and presentation of exogenous peptides. HLA linkage has been reported for several specific antigens in asthma, including Amb a V of ragweed and dust mite allergens. The T-cell receptor is also important in the recognition of foreign antigens. An analysis of 2 independent sets of families showed genetic linkages between IgE responses and microsatellites from the TCR-α/β region, but not from the T-cell receptor γ/δ area (8). Significant linkages were detected to this component of the T-cell receptor and sensitivity to house dust mite allergens, cat allergens, and total IgE. Although the function of the T-cell receptor for γ/δ cells has not been established, these cells are located on mucosal surfaces and may assume a key role in initiating IgE responses to environmental antigens (9).

Other genetically derived factors could influence T-helper (Th) cell development and its effects on IgE antibody synthesis. Bacterial antigens may favor the development of Th1 cells from CD4+ T cells through a CD14-dependent pathway (10). CD14 is constitutively expressed on monocytes and macrophages, is present in serum in a soluble form (sCD14), and maps to chromosome 5q31.1. Investigators have identified a C→T transition at bp –159 (CD14/–159) that may play a significant role in regulating serum sCD14 levels and total serum IgE. These findings point to the expanding complexity of factors regulating IgE synthesis and to an eventual linkage to the onset of asthma. Therefore, genes have been identified that can encode for 2 key processes in asthma: IgE synthesis and allergic inflammation. Whereas the presence of these genes establishes the susceptibility to develop asthma, the right environmental conditions occurring at the right time appear to be cofactors for the clinical manifestation of the disease.

Environmental factors influencing the production of allergic inflammation

Cytokines in the uterine environment. The uterus provides a unique immunologic environment that protects the fetus from being rejected by maternal allogenic T-cell (Th1) responses. Cytokines generated in the uterus are likely to orchestrate this protective effect. For example, it has been demonstrated that Th2-like cytokines (IL-4, IL-5, and IL-10) are produced in the uterus or amnion during gestation in both humans and rodents, and that these cytokines may serve to inhibit maternal cell-mediated immune responses that would otherwise be deleterious (11).

The same cytokines that may protect the fetus from cytotoxic immune responses could also affect the development of the fetal immune system. High levels of Th2-like cytokines (i.e., IL-4 and IL-10) could reduce secretion of IFN-γ and other Th1 cytokines from the fetus, which could then bias the developing neonatal immune system toward production of Th2-like cytokines and promote allergy. This concept is supported by studies of cytokine production from neonatal T cells, which have generally been found to produce relatively low levels of IFN-γ and to overproduce Th2-like cytokines. In addition, if maternal allergy causes a further deviation of the placental immune response toward Th2-like cytokines, this effect could explain why the risk of developing allergic disease in childhood is more closely related to maternal allergy than to paternal allergy.

In utero sensitization. There is experimental evidence to support the concept that allergen sensitization can occur in utero. First, several cases have been reported in which young infants developed allergic reactions upon their first ingestion of a specific food protein. Considering that IgE does not cross the placenta, one potential explanation for this phenomenon is that sensitization in utero occurs through traces of antigenic proteins that are present in the maternal circulation, cross the placenta, and sensitize fetal lymphocytes. To test this hypothesis, several studies have been conducted to detect neonatal allergen sensitization. In support of this concept, allergen-specific proliferative responses in cord blood lymphocytes have been demonstrated (12). Although these findings suggest that fetal lymphocytes can be activated by allergenic proteins in the maternal circulation, positive responses do not necessarily indicate allergy, and these activated lymphocytes could just be cells involved in tolerance. In older children, positive lymphocyte responses to allergens can be found in both allergic and nonallergic individuals, and they have not been found to be useful discriminators of allergy. Additional research is needed to clarify the significance and predictive value of lymphocyte responses in newborns.

Diet. Food allergy is often one of the earliest manifestations of atopy, and sensitization to food is a risk factor for the subsequent appearance of respiratory allergy and asthma. There have been numerous studies of the effects of dietary restrictions on the prevention of allergy and asthma, but the findings of many of these studies are limited by inadequate controls, length of follow-up, or
sample size. An earlier study examined the effects of combined maternal and infant dietary restrictions. In this study, infants with allergic siblings were identified, the mother’s diet was restricted (no milk, eggs, fish, beef, or peanuts) during the third trimester of pregnancy and lactation, and infants were either exclusively breast-fed for 5–6 months or ate an unrestricted diet (13). At the 1-year follow-up visit, the group of children with the restricted diet tended to have a lower prevalence of eczema, and if eczema was present, its severity was significantly reduced.

In a larger prospective study, children of atopic parents were randomly assigned into an intervention (n = 103) or control (n = 185) group and completed a 2-year evaluation (14). The intervention consisted of maternal avoidance of milk, eggs, and wheat, with limited soy and wheat intake during breast feeding. Children in the intervention group had less atopic dermatitis and food allergy at 1 year of age, and allergy to cow’s milk was reduced through 2 years of age. By age 7, there were no group-specific differences in the period prevalence of eczema and food allergy. Because of effects before the age of 2 years, the cumulative prevalence of food allergy remained lower at age 7, suggesting that the interventions did more than just delay the onset of food allergy, and actually prevented some cases. Notably, changes in the infant diet did not reduce the incidence of allergic rhinitis and asthma by the age of 7 years.

Whether or not breast feeding can prevent childhood allergy has been debated since the 1930s, when it was reported that breast-fed infants were at lower risk for developing asthma compared with infants that were fed cow’s milk. Although numerous studies have thus far failed to resolve this issue (15), several points are clear. First, because of multiple beneficial effects on growth, development, and the immune system, breast milk is the ideal infant diet and should be advocated regardless of the allergic history of the family. Second, food proteins consumed by the mother can be detected in breast milk, and this low level (nanogram quantities) of food protein is sufficient for causing allergen sensitization and inducing allergic symptoms in a subset of allergy-prone infants.

**Infections**

During infancy, certain viruses have been implicated as potentially being responsible for the inception of the asthmatic phenotype. Infections with respiratory syncytial virus (RSV) or parainfluenza virus (PIV) have received much attention because of their predilection for producing a pattern of symptoms termed bronchiolitis, which parallels many of the features of childhood and adult asthma. RSV causes about 70% of these episodes, and it is estimated that, by 1 year, 50–65% of children are infected with this virus (16); 40% of these infections involve the lower respiratory tract. Children aged 3–6 months are the most prone to developing lower respiratory tract symptoms, suggesting that a developmental component (e.g., lung and/or immunologic maturation) may be involved as well.

The relationship between RSV infections during the first year of life and the subsequent development of the asthmatic phenotype has been the subject of both interest and controversy. Variations in reporting longitudinal outcomes (e.g., recurrent wheezing, measurements of airway hyperresponsiveness, and diagnosis of asthma) appear to be influenced mostly by the criteria used to define bronchiolitis. These criteria include the type of virus producing the symptoms (in addition to RSV, PIV, coronavirus, influenza virus, and rhinovirus can cause bronchiolitis in this age group; ref. 17); the age at the time of infection; the nature and severity of symptoms required for inclusion; and, finally, the characteristics of both the study population (community versus hospital-based) and the study design (retrospective versus prospective). A number of long-term prospective studies of children admitted to a hospital with documented RSV-induced bronchiolitis have shown that about 75% will experience wheezing in the first 2 years after the initial illness, more than 50% will still wheeze 3 years later, and approximately 40% continue to wheeze after 5 years.

Recently, additional insight into these areas has been provided by the results of an 11-year prospective study involving 880 children who were enrolled at birth, followed for the development of lower respiratory tract illnesses (LRIs) in the first 3 years of life, and then evaluated for the presence or absence of physician-diagnosed asthma and/or a history of current wheezing at ages 6 and 11.

**Figure 2**
The early life origins can be divided into a number of phases. Early life events can lead to the development of a Th2-like environment, which is influenced by infections (Th1) rather than allergen exposure, diet, and certain respiratory infections. The tendency toward a Th2-like setting will promote the likelihood of IgE production toward environmental allergens. With sensitization, there can be the development of acute airway inflammation, then persistent inflammation, and eventually airway injury and remodeling.
RSV may also influence Th1/Th2 responses. In hospitalized infants (1–15 months of age) with an acute lower respiratory tract infection caused by RSV, there was a suppression of their IFN-γ production, and, although IL-4 production was also decreased, the IL-4/IFN-γ ratio was significantly increased. In another study of infants hospitalized with bronchiolitis, blood samples were obtained at the time of illness and 5 months later (23). Infected patients had an increased percentage of CD4+ , CD25+ , and CD23+ lymphocytes at the 5-month follow-up. Plasma IL-4 levels, although initially not different from those in control patients, increased significantly in the infected children 5 months later. Blood lymphocytes, obtained during the time of bronchiolitis, produced less IFN-γ in response to IL-2 in children who went on to develop a pattern of recurrent wheezing. Peripheral blood lymphocytes from infants who had persistent wheezing produced more IL-4 in response to Dermatophagoides farinae antigen (23). Finally, lower IFN-γ production at the time of bronchiolitis has been demonstrated to be an indicator of reduced pulmonary function and increased responsiveness to histamine 4.9 months after bronchiolitis, and was related to the development of asthma after bronchiolitis in infants (23). Therefore, early evidence demonstrates an association between decreased IFN-γ responsiveness and/or increased IL-4 elaboration and asthma-like parameters such as recurrent wheezing and airway hyperresponsiveness. Unfortunately, the pattern of cytokine response that these infants displayed before infection was not evaluated. Thus, it is impossible to know at present if the observed results represent cause and effect, or merely reflect intrinsic predispositions to diminished Th1 and/or enhanced Th2 responses.

Antigen-specific T cells and antibody-producing B cells are both formed in response to viral infection. T-cell responses mainly involve the induction of antigen-specific cytotoxic CD8+ cells, which have the capability of lysing target cells sharing MHC class I molecules complexed with viral peptides. CD8+ T cells produce both IFN-γ and TNF-β, a predominant Th1 cytokine profile. In contrast, CD4+ cells that facilitate antibody responses can be divided into Th1 and Th2 subsets based on the cytokine profile that various clones produce. However, there is increasing evidence that CD8+ T cells may also elaborate Th2-type cytokines, thereby increasing their ability to regulate various immunoinflammatory processes. This subset of CD8+ T cells has been referred to as Tc2. From a number of observations, it is clear that the cytokine profile a given T cell will produce is significantly influenced by the cytokine milieu that is present during stimulation. For example, in the presence of IL-4, CD8+ T cells may switch to a predominant Th2 type of response. Similarly, in a transgenic murine model investigating the interactions of atopy and viral infection, it was shown that local bystander Th2 responses mediated by CD4+ T helper cells (induced by allergen exposure) switched virus-specific CD8+ T cells from producing IFN-γ to producing IL-5 (24). In addition, when these IL-5–producing cells were then challenged with virus peptide, a significant degree of pulmonary eosinophil infiltration occurred. If similar relationships are present in humans, it is conceivable that a tissue background rich
in Th2 cytokines in atopic patients could influence the type of T-cell cytokine response that may occur after viral inoculation. This augmented Th2 response could then significantly influence the characteristics of the immunoinflammatory airway response. This immune bias, coupled with the diminished IFN-γ production noted after RSV infection, could begin the process of imprinting a particular type of immune response to viruses or allergens that would ultimately result in persistent airway inflammation and the induction of the asthmatic phenotype.

To evaluate more comprehensively the relationships among viral infection, atopy (cytokine dysregulation or Th1/Th2 imbalance), and immunological and/or lung developmental components, a rat model of virus-induced airway dysfunction has been studied extensively (25). In this model, infection with type 1 PIV during a critical developmental time period (when the animals are weaning [3–4 weeks of age] as opposed to when they are neonates [4–5 days] or adults) produces chronic (8–12 weeks after infection), episodic, reversible airway inflammation and remodeling. This response was associated with alterations in airway physiology (increased resistance and methacholine responsiveness) that resemble human asthma, and was seen in high (Brown Norway strain), but not low (F344 strain), IgE antibody–producing animals (26). The temporal progression of this asthma-like syndrome is associated with a Th1/Th2 imbalance within the lung, and its development can be significantly attenuated by the exogenous administration of IFN-γ just before, and during, the viral infection in the Brown Norway responder animals (27). These studies support the concept that, in addition to genetic (atopy and cytokine dysregulation or imbalance) and environmental (virus infection) factors, developmental issues are important determinants of the asthmatic phenotype. They also highlight the presence of important windows in time that determine the outcome of host-environment interactions.

Allergic sensitization as it relates to asthma

Asthma in children is strongly linked to the development of respiratory allergy. Nearly 90% of children with asthma have respiratory allergies, with indoor allergens, house dust mite, Alternaria, cockroach, or cat most closely associated with childhood asthma (28). In addition, a strong correlation exists between the number of positive skin tests in children and the severity of asthma (29). Finally, the intensity of exposure to house dust mite protein during infancy has been shown to lead to an earlier onset of asthmatic symptoms in children (30). These observations strongly suggest a causal relationship between allergy and the origins of asthma.

To examine this hypothesis, it is logical to evaluate the temporal sequence of allergy and asthma. Sensitization to food proteins can occur in the first year of life, followed by sensitization to perennial respiratory allergens beginning at 2–5 years of age. Most children with asthma experience their initial episode of wheezing in the first 3 years of life, and these illnesses are primarily associated with viral infection (31). Moreover, those children who develop respiratory allergy after a viral-induced episode of wheezing are at greater risk for developing chronic asthma (31). Determining the age of onset for asthma can be enigmatic, given the ambiguous transition between viral-induced wheezing and chronic airway obstruction and hyperresponsiveness that often occurs during the first 6 years of life. Thus, the exact sequence of allergen sensitization and onset of asthma is difficult to establish. Nonetheless, it is clear that the first 6 years are a critical time period in this respect, and that the processes leading to asthma may be evolving simultaneously. Although these observations are compatible with a cause and effect relationship, they do not exclude the possibility that asthma and allergy are 2 closely related phenomena that develop as a consequence of related genetic and environmental influences.

Several epidemiologic studies demonstrate that the season of birth influences the subsequent development of respiratory allergy. Children born in the spring are at increased risk for developing birch and grass allergy, whereas those born during ragweed season have an increased risk of ragweed allergy. These observations suggest that there may be a period during the first few months of life in which the immune system is particularly susceptible to developing Th2-like T-cell responses to certain inhaled allergenic proteins. This concept is especially intriguing when one considers the temporal sequence of this process; the early exposure to allergenic proteins initiates a process that is not clinically evident for several years, as pollen allergy is rarely diagnosed until children have reached school age. These findings, along with data derived from experimental models of sensitization in animals, suggest that early exposure to inhaled proteins initiates allergen-specific T-cell responses. However, additional elements in the immune system, such as dendritic cells or other antigen-presenting cells, must mature before allergy to these proteins can develop. Alternatively, the initial allergen-specific T-cell responses may require repeated restimulation, and the intermittent nature of pollen exposure could explain why hay fever takes longer to develop than allergy to foods or perennial inhalants.

Effects of smoking and pollution

Active or passive exposure to smoke is associated with an increased incidence of many respiratory disorders, including asthma and allergic rhinitis (32). The effects of cigarette smoking on fetal pulmonary development are also manifold. Smoking causes lower birth weights and corresponding reductions in lung size, and small lung size has been identified as a risk factor for wheezing lower respiratory illnesses in infancy. In addition to decreasing lung size, in utero exposure to tobacco smoke has been shown to reduce newborn lung function. To study the effects of tobacco on infant pulmonary function, the time to peak tidal expiratory flow, as a proportion of the total expiratory time, has been measured (T_{PEF}/T_{E}). This index measures slowing of expiratory flow by the combination of glottic narrowing and diaphragmatic tone and is reduced in adults with obstructive airway disease (33). Using these techniques, mild airway obstruction has been detected in infants born to smoking mothers within 3 days of
birth, strongly suggesting that smoking causes reduced pulmonary function in the developing fetus. This concept is further supported by a study that evaluated pulmonary function before discharge in 108 preterm infants, 40 whom were born to mothers who smoked during pregnancy. Decreased T_{PEF}/T_{E} was associated with exposure to tobacco smoke in utero, but not with birth weight or length; this relationship persisted in the multivariate analysis. Together, these studies provide compelling evidence that maternal cigarette smoking can harm developing lungs both before and after birth, and that these effects are likely to contribute to an increased risk of developing wheezing with viral infections, and eventually chronic asthma.

The effect of outdoor air pollution and asthma and allergies is more controversial. Epidemiologic evidence linking increased rates of allergy and asthma to the urban environment, and even the proximity of the home to major highways, suggests that air pollution enhances allergic sensitization (34). In addition to these findings, there is new experimental evidence that diesel particles, and perhaps other pollutants as well, act as adjuvants to enhance production of Th2-like cytokines and IgE production in cell culture and in the human in vivo (34). However, a large study conducted in Germany shortly after the country’s reunification contradicts these findings (35). German schoolchildren with very similar genetic backgrounds, but from 2 different environments, were evaluated for allergic sensitization and respiratory diseases. One group of children resided in Munich in the former West Germany. The other group was from Halle, a city in the former East Germany with high levels of air pollution resulting from the burning of high-sulfur fuels in home-heating furnaces. Although the total incidence of respiratory disease was greatest in the group from Halle, asthma and skin-test positivity were nearly 3-fold higher in the Munich schoolchildren. This study, like others, indicates that there are factors associated with the Western lifestyle that increase the risk for developing asthma and allergy. Furthermore, in this study, pollution did not seem to be associated with increased asthma or allergy. Clearly, air pollution is a complex entity, and it seems likely that individual pollutants may have divergent effects on the risk for developing allergy. Additional information is needed to determine the effects of specific pollutants or combinations of pollutants on rates of allergen sensitization.

Summary

It is increasingly clear that the seeds of the asthmatic diathesis are planted early in life, possibly in utero. The cellular and molecular events that are responsible for these important disease processes are only now being identified. Genetic factors play a crucial role. In addition, the in utero microenvironment and neonatal immune system are now appreciated to be intrinsically skewed toward a Th2 (rather than Th1) immune response. When the genetically predisposed individual then encounters key environmental factors, an immune/inflammatory response ensues that ultimately directs the development of allergic disease and, through processes not fully defined, focuses these immune-regulated inflammatory responses into the lower airway (Figure 2). A variety of levels of investigation suggest that there are crucial temporal windows in babies and children during which these important patient-environment interactions need to occur for full disease expression, and that a variety of agents, including respiratory infections, diet, and toxin exposure, can all interact to regulate the final phenotype. The culmination of these multiple events is the development of Th2-like inflammation, bronchial hyperresponsiveness, and air flow obstruction/clinical asthma. The appreciation that these events begin early in life has refined our thought processes regarding disease pathogenesis, and has provided new experimental targets for investigators. Hopefully, an enhanced understanding of the pathogenesis of childhood asthma will provide the types of insights that will allow us to think in terms of primary disease prevention rather than the present goal of secondary symptom amelioration.

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