The Childhood Origins of Asthma (COAST) study


Although asthma is probably a heterogeneous disease or syndrome, three factors and/or events consistently emerge for their ability to significantly influence asthma inception in the first decade of life: immune response aberrations, which appear to be defined best by the concept of cytokine dysregulation; lower respiratory tract infections, in particular respiratory syncytial virus (RSV); and some form of gene–environment interaction that needs to occur at a critical time-period in the development of the immune system or the lung. It remains to be firmly established, however, how any one or all of these factors, either independently or interactively, influence the development of childhood asthma. For example, cytokine dysregulation (T helper 1/T helper 2 imbalance) appears to track best epidemiologically with allergic diseases. As not everyone who undergoes allergic sensitization develops asthma, some other host–environment interaction must need to occur to target this chronic allergic inflammatory response to the lower airway. Some evidence suggests that this event might be an environmental insult in the form of a virus infection, particularly with RSV, which has a predilection for infecting, destroying, and/or in some way biologically altering lower airway epithelium. However, only a fraction of children develop recurrent wheezing following RSV infections, despite the fact that nearly all children have been infected at least once by 2 years of age. Thus, although RSV infections may have the potential of targeting the inflammatory response to the lower airway, they may only be able to do so during a vulnerable time-period during development of the immune system or lung. This developmental component may further reflect important gene–environment interactions that regulate both short- and long-term airway physiological alterations that manifest themselves clinically as childhood asthma. Efforts to determine and define the importance of these three factors to asthma pathogenesis are the focus and goal of the COAST (Childhood Origins of Asthma) project.

From prospective epidemiological evaluations, for many individuals the asthmatic phenotype had its roots in the first few years of life. In infants and children, wheezing illnesses associated with lower respiratory tract infections have been noted in \( \approx 50\% \) of patients by 6 years of age (1). Based on the time of onset and pattern of wheezing symptoms, these children have been grouped into at least three phenotypes: transient wheezers (present in the first 3 years, gone by 3 years of age); persistent wheezers (present in the first 3 years and still present beyond 3 years of age); and late-onset wheezers (not present in the first 3 years, but symptoms begin between 3 and 6 years of age) (1). Both virus-specific and host-specific factors may contribute to the clinical expression of these phenotypes. Virus-specific factors include the ability to induce virus-specific immunoglobulin E (IgE) antibody [e.g. respiratory syncytial virus (RSV) (2,3) and parainfluenza virus (4)], and the
type of cytokine response to various viral peptides (e.g. G vs. F proteins of RSV) (5) or viruses [interleukin (IL)-11 responses to asthma-associated viruses] (6). Host-specific factors which appear to be important in the transient wheezing phenotype are primarily lung size (7), while in the persistent wheezing phenotype, risk factors include exposure to passive smoke, a maternal history of asthma, and an elevated serum IgE level obtained at 9–12 months of age (1,8–11). Interestingly, the prevalence, at age 6 years, of allergic sensitization, is increased in both the persistent and late-onset wheezing phenotypes, but serum levels of IgE are only increased in the persistent wheezing phenotype when evaluated at 9 months of age (1). These latter relationships suggest that gene–environment interactions may be contributing to the expression of these two phenotypes.

Of the various risk factors which may influence the development of persistent wheezing and asthma, two are most often implicated: first, the presence of atopy in the host (genetic); and second, the development of lower respiratory tract infections (environmental) (12–14). At present, however, the relative importance of these two factors is uncertain owing to a paucity of prospective longitudinal analyses. From the available information, however, interactions between these two factors appear to be bi-directional and dynamic in that the atopic state can influence the lower airway response to viral infections (1,15), viral infections can influence the development of allergy (16–18), and interactions can occur when individuals are exposed simultaneously to both allergens and viruses (19–21). Some (16), but not all (14), investigators have noted that infantile RSV infections increase the risk of allergic sensitization later in childhood. These divergent findings in terms of clinical outcomes may be related to the severity, etiology (i.e. RSV vs. other respiratory tract viruses) and/or timing (developmental component) of the initial infection in relationship to allergen exposures (22). Prospective studies designed to address the contribution of each of these factors to childhood asthma pathogenesis are obviously needed.

What is the relationship between viral infections and asthma?

Acute viral infections have been demonstrated to be temporally associated with a number of important clinical consequences (23), including: the development of wheezing-associated illnesses in infants and small children (24–31); initiating acute exacerbations of asthma, in both children and adults (24,28,32,33); and inducing short- and long-term alterations in airway physiology, such as increasing airway responsiveness (34) and creating abnormalities in airflow (35), lung volumes (36,37) and gas exchange (38). Recent prospective observations have demonstrated that certain viral infections, especially RSV, may also contribute to the inception of childhood asthma in the first decade of life (14,39).

Do RSV infections contribute to asthma inception?

In infants, infection with RSV has received much attention because of its predilection to produce a pattern of symptoms termed ‘bronchiolitis’, which parallel many of the features of childhood and adult asthma (12). During 1980–96 in the USA, rates of hospitalization of infants with bronchiolitis increased substantially, as did the proportion of total and lower respiratory tract hospitalizations associated with bronchiolitis (40); RSV caused $\approx 70\%$ of these episodes. However, RSV bronchiolitis represents only the most severe fraction of cases, in that by 1 year of age, 50–65\% of children will have been infected with this virus and, by 2 years of age, nearly 100\% (41). Children 3–6 months of age are most prone to develop lower respiratory tract symptoms, suggesting that a developmental component (e.g. lung and/or immunological maturation) may also be involved (41). Although controversy exists regarding the relevance of antecedent RSV infections and the development of recurrent wheezing (42), a recent long-term prospective study of large numbers of children has demonstrated that RSV infections are a significant, independent risk factor for subsequent frequent wheezing, at least within the first decade of life (14,16). It remains to be established, however, how RSV infections produce these outcomes, owing to the fact that virtually all children have been infected with this virus before their second birthday.

Are cytokine responses dysregulated in children with allergies and/or asthma?

Recent observations have stimulated research efforts to further define the relative importance and pathophysiological contributions of cytokine dysregulation [the so-called Thelper 1/Thelper 2 (Th1/Th2) imbalance] to the development of various atopic phenotypes, including asthma (43). Although questions remain as to the full impact of a Th1/Th2 dysregulation in established asthma, the contribution of cytokine polarization to the inception and evolution of various atopic diseases, including asthma, has received more uni-
form support. At birth, largely as a result of placentally derived Th2 trophic factors, cytokine profiling of cord blood indicates that the newborn infant’s mononuclear cell response is skewed towards a Th2-like phenotype (production of IL-4, IL-5, IL-6, and IL-10) (44). The relative nature of this Th1/Th2 imbalance [as reflected by diminished interferon-γ (IFN-γ) production] may be a predictor of the subsequent development of allergic disease and/or asthma (44–47).

In children who are destined to be at increased risk of developing allergic diseases and/or asthma, a further diminution in cord blood mononuclear cell generation of IFN-γ (46,48) and IL-13 (49) has been noted, and the capacity of these children to generate normal IFN-γ responses lags behind a non-atopic control population (44,50,51). Although in the first decade of life these differences eventually become less evident, the IFN-γ response curve is shifted to the right in the first few years of life for atopic children (lymphocytes from atopic children produce significantly less of this cytokine in comparison to lymphocytes from non-atopic children). These observations indicate that there may be a critical time-period in the development of the atopic child in which target organs, such as the lung, may be particularly vulnerable to environmental stress factors such as viral respiratory tract infections. While these observations have generated intense interest in the intrauterine/neonatal, genetic, and environmental influences, conflicting results have prevented the establishment of any firm conclusions (52). Therefore, well-designed prospective studies are needed to address these various factors and their interactions.

The COAST (Childhood Origins of Asthma) study

To study the contribution of, and the interactions among, age, patterns of cytokine secretion and virus infections, with respect to the subsequent development of childhood asthma, a cohort of children (n = 287) who are at increased risk of developing asthma (at least one parent has allergies and/or asthma) were enrolled at birth to participate in a prospective study designed to address these issues. The following research hypothesis is the primary focus of the COAST study (Fig. 1), namely that the development of the persistent wheezing phenotype in children, or childhood asthma, requires the presence of at least two factors at a critical time-point in the development of the immune system or lung. These two factors are as follows:

1. dysregulation of cytokine responses at birth (genetic factor); and

2. development of a clinically significant lower respiratory tract viral infection (primarily RSV bronchiolitis) (environmental factor).

The COAST study was funded by the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD) in September 1998 and launched in November of that same year. The COAST hypothesis evolved from data generated in a rat model of virus-induced airway dysfunction developed in collaboration with Dr. William Castleman and presently used within our laboratories (53–56), as well as from data reported in humans. Taken together, these findings led to the ‘two-hit’ hypothesis (a restatement of the research hypothesis stated already) Cow’s milk protein allergy/intolerance (Fig. 2) pertaining to the inception of childhood asthma. Cytokine dysregulation, potentially present at birth, is influential in determining the host response to viral infections. For example, if an infection occurs with a particular virus (i.e. RSV) at a critical time-period (i.e. infancy), the combination of cytokine dysregulation and RSV infection has a...
significant probability of producing the clinical syndrome of bronchiolitis and, over time, the development of a persistent wheezing phenotype or asthma. In contrast, infants and children who have demonstrable cytokine dysregulation, but do not develop an infantile RSV infection, have an increased probability of developing allergic sensitization, including asthma, which may have its initial presentation in later childhood or adolescence. In children with normal cytokine regulatory patterns, RSV infections can produce both upper and lower respiratory tract illnesses (the latter being more common in premature infants or in term infants with diminished pulmonary function at birth), but the wheezing and coughing which may be associated with these infections resolve over time.

Based on sample-size calculations to address this hypothesis, a total of 146 children at high risk of developing allergies and/or asthma needed to complete the study in order to obtain 70% power to detect a log-odds ratio of 2.2 (odds ratio ¼ 9.0) in favor of development of the persistent wheezing phenotype for the double-factor group (cytokine dysregulation and RSV infection), relative to the other groups, with a one-sided test statistic having a 5% Type I error rate. The test statistic is the interaction test for a logistic regression model, and sample size and power formulas were derived using the formula for the variance of the associated logistic-regression parameter estimate (57). Community interest in the project far exceeded initial expectations and enrolment was expanded to 312 consenting families. Of these 312 babies, 287 children are still actively enrolled. The remaining 25 were excluded for the following reasons: 14 cord blood failures; four withdrawals; two genetic abnormalities; one respiratory distress syndrome; and four non-allergic parents (the mothers were not skin tested until after delivery).

To be eligible for study participation, either the expectant mother (31.3 ± 4.8 years) or father (32.9 ± 5.3 years) had to be allergic (defined as one or more positive aeroallergen skin tests), asthmatic (defined initially historically), or both. The distribution of these parental phenotypes was as follows: 44.5% allergy only; 1.8% asthma only; 37.7% allergy and asthma; and 16% neither (the other parent qualified the child for participation). Infants needed to be born at term (mean birth weight ¼ 3.51 ± 0.5 kg; head circumference ¼ 34.7 ± 2.3 cm; 56.4% male and 43.6% female gender; 86.8% Caucasian and 13.2% ethnic minority) (month of birth amortized evenly over a 1-year cycle), have Apgar scores of at least 7 at 5 min (8.9 ± 0.49), and not have any significant neonatal respiratory difficulties or anomalies that would preclude them from participating fully in the study.

To address the experimental hypothesis, we are in the process of performing in vitro evaluations of cytokine response patterns in the children at birth and at 1, 2, and 3 years of age, and also in their parents, and defining viral respiratory pathogens responsible for significant lower respiratory tract illnesses throughout the first 3 years of life. Thus far, >3000 nasal mucus specimens have been obtained in protocol-initiated visits and during respiratory illnesses of sufficient severity to dictate specimen collection, according to a predefined symptom-severity scoring system. We further plan to evaluate these variables over time (developmental aspect), and to determine the relative contribution of these factors in influencing the development of various wheezing phenotypes during early childhood. In the past 2.5 years, we have made considerable progress in evaluating this hypothesis (58–68). However, because the development of the persistent wheezing phenotype cannot be ascertained until children enrolled in the COAST project reach at least 3 years of age, the major outcome measure cannot be evaluated prior to November 2001. Once the cohort reaches this landmark, we will be in a strong position to evaluate comprehensively and prospectively the contribution(s) of cytokine dysregulation, viral infections, and the timing of these events with regard to immune system and lung development with the development of various wheezing (asthmatic) phenotypes in childhood.

Acknowledgments

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References


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