Meeting report

Early immune development, atopy and asthma: insights from ATS 2001, May 18–23, San Francisco

Christian H Schroeter and Patricia W Finn

Pulmonary Division, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence: Patricia W Finn, Pulmonary Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel: +1 617 278 0704; fax: +1 617 264 6341; e-mail: pwfinn@rics.bwh.harvard.edu

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Abstract

There is rising evidence that the initiation of atopy and asthma may occur in early life or even during fetal life. At the American Thoracic Society meeting 2001 in San Francisco, multiple reports addressed epidemiological and immunological factors and their influence on the early immune system, as well as the development of atopy and asthma. Epidemiologic studies presented at the meeting suggest a protective effect of farming and pet exposure. Early-life exposure to endotoxin, a cell wall component of Gram-negative bacteria which can be found in high levels in the presence of pets, may have a protective effect. Investigations of the mechanism of the early immune system indicate that mononuclear cord blood cells have the ability to mount a lymphoproliferative response to mitogens and allergens. Reports suggest, however, that the validity of Th1/Th2 paradigm may need to be scrutinized in early human immune responses, particularly regarding the assumption that the neonate immune system is Th2 skewed. The prospective longitudinal follow-up of these studies is promising to give further insight into risk and protective factors in the development in atopy and asthma.

Keywords: asthma, children, endotoxin, immune response, neonatal

Introduction

Recent evidence suggests that the initiation of atopy and asthma may occur early in life, even prenatally. To identify environmental and genetic risk factors, several epidemiological studies are underway. In parallel, studies are investigating the mechanisms of early onset of atopy and asthma. At the American Thoracic Society meeting 2001 in San Francisco, multiple reports addressed epidemiological and immunological factors and their influence on the early immune system and the development of atopy and asthma. While not comprehensive, this report provides a brief summary of selected presentations on these topics, focusing on human studies.

Review

Risk and protective factors

Environmental factors, whether indoor or outdoor, are under investigation to determine their role in the initiation of atopy and asthma. Whether certain factors are protective or are, in fact, risk factors forms the basis of the studies described below.

Breast-feeding

The protective effect of breast-feeding against the development of allergy and asthma remains controversial. Dell *et al* (Hospital for Sick Children, Toronto, Canada) compared two groups of Canadian children less than two

CBMC = cord blood mononuclear cell; IFN = interferon; IL = interleukin; NF = nuclear factor; RSV = respiratory syncytial virus; Th = T-helper cell; TNF-α = tumor necrosis factor-α.

years of age for the onset of asthma and wheeze. The prevalence of asthma increased over time, while the prevalence of wheeze remained the same. Concomitant with an increase in the prevalence of breast-feeding, both prenatal and postnatal maternal smoking decreased significantly. A protective effect of breast-feeding against asthma as well as against wheeze was shown with increasing duration of breast-feeding. While this study suggests a short-term effect of breast-feeding on the development of atopy and asthma, the long-term effects will need to be addressed [1].

Pets and endotoxin exposure

To examine the relationship between pets, vermin and endotoxin in house dust, Heinrich *et al* (GSF Neuherberg, Munich, Germany) investigated the homes of German children aged 5–10 years. Endotoxin concentrations in dust samples were significantly increased with the presence of dog, cat and cockroach. The authors conclude that having dogs or cats in the home is consistent with higher exposure to endotoxin. Also, based on previous reports of protective effects of cats or dogs on the development of atopy, endotoxin exposure may contribute to a lower risk of atopy in later life [2].

Exposure to pets in the first year of life and the impact on atopy and lung function was investigated by Ownby *et al* (Henry Ford Hospital, Detroit, MI, USA). Interestingly, exposure to two or more animals (cats or dogs) was associated with a significantly lower prevalence of any positive skin test and any allergen-specific IgE at six to seven years of age. For boys only, exposure to two or more pets was associated with a lower total serum IgE, prevalence of methacholine responsiveness and better lung function. This also suggests a role for endotoxin as a protector in atopy and, particularly in boys, leads to an improvement in lung function [3].

Litonjua *et al* (Channing Laboratory, Boston, MA, USA) presented results from a longitudinal study regarding association between house dust endotoxin levels and wheeze in young children. In their cohort the exposure to higher levels of endotoxin early in life is associated with increased wheezing episodes in children less than six years old. Their model, however, predicted a decreasing risk over time, concluding that endotoxin exposure may be protective against further wheezing episodes in children older than six years. This prediction supports the hypothesis of a protective effect of endotoxin, including dogs or cats as a reservoir of endotoxin [4].

Farming exposure

A cross-sectional study performed in European rural communities investigated the effect of farming. Braun-Fahrlander *et al* (Institute of Social Medicine, University of Basel, Switzerland) reported that the timing and the duration of exposure to stables, and consumption of farm milk during the first year of life, are essential for a strong protective effect against the development of asthma, hay fever and atopic sensitization. While maternal exposure has an independent effect, the role of exposure during pregnancy as well as the effect of breast-feeding in this study has not been evaluated. The authors speculate that farming exposure may be a surrogate marker for other types of microbacterial exposure like endotoxin. As endotoxin levels are increased in stables this report suggests that endotoxin exposure is a protective factor against the later onset of atopic diseases [5].

Timing of sensitization in early childhood

Exploring patterns of atopic sensitization in association with childhood asthma, Illi *et al* (Dr von Haunersches Kinderspital, Munich, Germany) presented results from the German Multicenter Allergy Study. The investigators found that an early sensitization to food allergens before the age of two is only associated with asthma at the age of seven when a subsequent sensitization to inhalant allergens occurs. Also, a positive parental history of asthma or allergy must be present. The authors conclude that an underlying factor pertaining to asthma and maternal transmission may determine both a certain pattern of sensitization and the later expression of an asthmatic phenotype [6].

Cord blood response profiles

Recent studies addressing the onset of atopy and/or asthma have also focused upon the developing immune system. Specifically, these studies have used the approach of examining functional immune responses in relationship to the later development of atopy and asthma. In the Th1/Th2 paradigm these diseases are thought to be Th2 skewed. Furthermore, pregnancy and the neonatal immune response are described as Th2-dominated. Conflicting data for the Th2 paradigm in the neonatal immune response will be presented in the following reports. Additionally one study investigated the expression of phenotypes combined with functional studies in cord blood mononuclear cells (CBMCs).

Cytokine profile in cord blood mononuclear cells and risk for viral infections

The association of cord blood cytokine response profiles after mitogen stimulation and infection with respiratory syncytial virus (RSV) in the first year of life was examined by Meyer *et al* (University of Wisconsin, Madison, WI, USA). Children who developed viral infection in the first year of life had a significantly reduced interferon (IFN)-γ/IL-13 ratio. RSV-positive respiratory infections showed primarily a relationship to IL-13 responses. A significant relationship between the absolute level of IL-13 and the incidence of RSV-associated lower respiratory tract infections was found. The authors conclude that a diminished mitogen-induced CBMC production of IL-13 may characterize infants who are at risk of developing RSV-associ-

ated lower respiratory tract infections during infancy. This cohort will be of special interest when examining the longitudinal follow-up of RSV infections in early life as it will provide a predictor of wheezing and development of atopy in later life [7].

Interleukin-12 production in cord blood mononuclear cells

IL-12, as an inhibitory cytokine for Th2 responses and a promoter for Th1 development, can increase cytotoxic T-lymphocyte responses and induce IFN-γ synthesis. To investigate IL-12 synthesis in humans, Upham *et al* (Institute for Child Health Research, Perth, Australia) examined IL-12 p70 production by CBMCs, five-year-old children and adults following stimulation with lipopolysaccharide and IFN-γ. They found a markedly reduced production of IL-12 p70 in CBMCs and peripheral blood mononuclear cells (PBMCs) from five-year-old children compared to PBMCs from adults. In contrast, cord-blood-derived dendritic cells synthesized comparably high levels of IL-12 [8].

Interleukin-4 and IFN-γ production in cord blood mononuclear cells

The production of IL-4 and IFN-γ in cord blood and infant cells was investigated by Halonen *et al* (University of Arizona, Tucson, AZ, USA). IL-4 and IFN-γ levels from CBMCs and mononuclear cells from infants aged two months and PBMCs from their mothers were investigated. The report showed a substantial reduction in the level of both cytokines in the infants compared to their mothers. Furthermore, IFN-γ production was directly related to IL-4 production in all samples. The authors conclude that these data indicate a remarkable tendency to maintain an IL-4/IFN-γ balance in infancy [9].

Interleukin-5 production in cord blood mononuclear cells

Miller *et al* (Columbia-Presbyterian Medical Center, New York, USA) compared mitogen-induced and allergen-induced proliferation and cytokine production of CBMCs in a cohort of Dominican and African Americans in New York. CBMCs had a significantly higher production of IL-5 in the presence of mitogen, cockroach, house dust mite or mouse antigen than in the absence of these. In response to dust mite, however, IL-5 and IFN-γ production increased in specific association with T cell proliferation. The cohort will be followed to investigate clinical correlation [10].

Phenotypic and functional characteristics of cord blood mononuclear cells

Looking at phenotype expression in CBMCs, Contreras *et al* (Brigham and Women's Hospital, Boston, MA, USA) reported up-regulation of CD4 after mitogen stimulation. CD45RA (memory cell marker) and CD45RO (naïve marker) were significantly up-regulated. Also, several samples showed a lymphoproliferative response to allergens such as cockroach (Bla g2) and house dust mite (Der f1) and produced IL-10, IL-13, IFN-γ and tumor necrosis factor-α (TNF-α). This report indicates that CBMCs can develop a mitogen-induced mature phenotype and they have the ability to respond to common aeroallergens with the production of both Th1 and Th2 cytokines [11].

Activation of transcription factors in cord blood mononuclear cells

Our own study (Schroeter *et al*, Brigham and Women's Hospital, Boston, MA, USA) investigated CMBCs for proliferative responses, cytokine production and regulation of the transcription factor NF-κB, a pivotal transcription factor in the inflammatory response. Comparing protein-DNA binding of nuclear extracts derived from mitogen-induced CBMCs with nuclear extracts from uninduced CBMCs, we found differential regulation of NF-κB activation. Furthermore, there was no significant difference between samples with up-regulation of NF-κB and those with down-regulation of IL-5, IL-13, TNF-α and IFN-γ. Both cytokine patterns, Th1 (IFN-γ and TNF-α) and Th2 (IL-5 and IL-13) were present. All samples were able to mount a mitogen-induced proliferative response. These data support the conclusion that CBMCs have a functionally intact immune response, which might be more complex than the Th1/Th2 paradigm. This cohort will provide the potential to correlate clinical data and immunological findings in a longitudinal follow-up [12].

Conclusion

Different approaches, epidemiological as well as immunological, have contributed further insights into the development of atopy and asthma. The recent presentations at the ATS meeting 2001 showed the important role of the early years for the development of the immune system and for the onset of atopy or asthma. Environment may play an important role in the priming of the immune system. Special interest was focused on exposure to endotoxin, which seems to exert both a protective effect as well as an increased risk for enhancing immune responses. The validity of the Th1/Th2 paradigm needs to be scrutinized in early human immune responses, particularly human cord blood immune responses shown in this review. Prospective follow-ups of these cohorts may provide important information for identifying and confirming known and novel biomarkers as risk or protective factors for developing atopy and asthma.

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