

EDITORIAL

Influence of maternal atopy on atopy in the offspring

Epidemiological studies over the last 30 years indicate that the prevalence of allergic disease is increasing in children and young adults [1]. Since the early work of Cooke and Vander Veer it has been known that atopic diseases run in families [2,3]; at the present time the general risk of allergy in the population is 20%; the risk when one parent is atopic is 50%, and 66% if both parents are atopic. Some, but not all, studies have shown an increased risk of atopy in children whose mothers are atopic. This maternal effect has also been seen in molecular genetic studies of asthma and atopy. This review explores those interactions between mother and offspring which influence the risk of atopy or asthma in the offspring.

Recent advances in cell biology and DNA technology have illuminated how the allergic inflammatory reaction is mediated by numerous cell interactions. The asthmatic airway is infiltrated with mast cells, eosinophils, macrophages, lymphocytes and plasma cells. It is now accepted that active T-cell immunity to common inhalant allergens is skewed towards T helper (TH) 2 cytokine phenotype; in contrast with the expression of TH1-skewed immunity in non-responsive normal subjects. It is thought that how those two different patterns of T-cell immunity develop in early life is pivotal to our understanding of the origins of asthma.

Since asthma is familial, it is possible that the influence of the atopic mother on her infant could be purely genetic. However, the genetics of atopy are complex and remain poorly understood. Genome-wide searches have shown that many genetic loci predispose to the disease [4]. Genetic influences probably fall into two types [5]. The first is the ability of the susceptible individual to recognize a common environmental allergen as foreign and initiate the allergic immune response. The second set of genetic influences regulate the overall cytokine response. Linkage of atopy to various chromosomes is reported [4] and these studies also show a strong maternal genetic influence on asthma development in the offspring. Unravelling the genetic basis of asthma is made more difficult by the lack of a single clinical phenotype. The expression of asthma also varies with age. There is evidence from cross-sectional epidemiological studies that persistent TH2 responders constitute the high-risk group for subsequent bronchial responsiveness and chronic asthma [6,7], although both skin test reactivity [8] and bronchial hyperresponsiveness [9] may decline with age. The heterogeneity of wheezy disorders is particularly striking in young children. Longitudinal studies which define the asthma phenotypes may provide the key to understanding how the interactions between genes and environment bring about disease.

Low concordance rate for asthma in studies of twins [10] strongly hints that environmental factors are important in the expression of disease. However, not all atopic subjects develop asthma. Although parental atopy, particularly maternal asthma, predicts childhood asthma, other factors such as maternal smoking and early life exposure to allergens are important [11]. Many studies have established the link between maternal smoking in pregnancy and asthma in young children. This subject has been reviewed [12]. Prospective studies using infant lung function tests suggest that the infants of cigarette-smoking mothers are born with small lungs. They show persistent lung function abnormalities in childhood with a propensity to wheeze on exposure to respiratory virus infections [13,14]. Longitudinal studies have shown that these wheezy toddlers lose their symptoms during childhood [13]; more persistent asthma in the older child is strongly associated with maternal asthma, hay fever and eczema.

Early life exposure to allergens postnatally may be a critical time for sensitization to occur. The development of atopic symptoms has been variably associated with the season of birth. In Finland, babies born just before the birch pollen season are more at risk for birch pollen sensitivity later in life [15]. House dust mite exposure in the first year is also a risk factor for asthma at 11 years [16].

Other early life experiences may be protective against atopic disorders, perhaps by tilting the infant's immune system towards a TH1 response. Large family size reduces the risk of hay fever in adult life [17]. The frequency of viral respiratory illnesses in infants in East Germany before reunification may explain the lower frequency of atopic disorders in the East European countries [18].

Prenatal influences on the unborn fetus are now the subject of intense interest. The fetal immune system develops early; lymphocytes are present in the fetal thymus at 7 weeks, and the fetal immune system is able to react to uterine factors by 15 weeks. Allergen-specific responses of the fetus have been studied by cord blood sampling. One study has looked at lymphocyte responses to food antigens as predictors of allergic disease [19]. A different group has shown that deficiency in interferon-gamma production by allergen-triggered cord blood cells predicts atopic eczema [20]. It is of interest that temporary immunoglobulin (Ig) E antibody formation is seen against cows milk and hen's egg in both atopic and nonatopic infants. In the infant genetically at risk, egg sensitization appears to be a risk factor for sensitization in childhood [21], and perhaps asthma in adults [22]. The pregnant mother may influence the immune system of her fetus in other immunological ways.

Transplacental priming of the T-cell system against environmental allergens appears relatively common and could, in the genetically predisposed infant, cause skewing away from the TH1 phenotype [23].

Some fetal exposures may be protective for later atopy. IgG crosses the placenta, and animal studies have shown that maternal IgG antibodies to ovalbumin can suppress the development of IgE antibodies in the offspring [24]. In a human study, fewer positive skin prick tests to grass were seen in 3–12-year-old children where mothers had undergone rye grass immunotherapy during pregnancy [25]. The children born to the treated mothers had higher IgG antibodies to rye grass than the children of untreated mothers. The influence of the atopic mother on her unborn child is demonstrated further by work reported in this month's issue of the *Journal*. Jenmalm and coworkers have studied the role of cord blood IgG antibodies to ovalbumin, β -lactoglobulin birch and cat antigen in relation to maternal atopy, and sensitization at the age of 8 years [26]. The study design was a birth cohort study of 96 children, 38 with an atopic mother, 22 with an atopic father and 36 with no parental history of atopy. Jenmalm and colleagues found that high levels of cord blood IgG subclasses, especially IgG4 antibodies to food and inhalant allergens, were associated with maternal atopy. High levels of IgG antibodies to inhalants, but not food allergens, were associated with less atopy in the same children examined at 8 years of age. This study is important for two reasons. It demonstrates that the atopic mother reacts in a quantitatively different way with a bias towards type 2 cytokine production. The other important observation is that maternal IgG antibodies do influence the immune responses of their offspring.

The implications may be far reaching and offer fresh light on previous epidemiological observations. If maternal inhalant IgG antibodies are protective this may be the explanation for the increased risk for allergy to seasonal allergens in children born before the relevant pollen season. The mother would not be exposed, and the cord blood would show low levels of specific IgG antibodies to birch pollen.

The fetal and neonatal immune system is influenced by a number of external factors. Downregulating the TH2 response (or upregulating the TH1 response) suggests attractive approaches to interventions in early life which might reduce the risk of asthma later. Intervention programmes on babies at risk are already popular, although prediction of risk remains imprecise. Allergen avoidance regimes in pregnancy and infancy [27] probably reduce or delay the onset of eczema but may not prevent asthma. Immunomodulation to stimulate the TH1 response remains attractive [28], but much more work on safety and efficacy are required before either approach can be recommended clinically. Meanwhile the pregnant mother must be advised to stop smoking.

References

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