

Key Factors in the Development of Asthma: Atopy

PATRICK G. HOLT

TVW Telethon Institute for Child Health Research, Perth, Western Australia, Australia

One approach to unraveling the role of the multiple risk factors that contribute to the development of asthma is to track the process in cohorts of children from birth until age(s) at which the disease manifests. In relation to atopy, this involves the prospective and cross-sectional study of allergen-specific T cell function in cohorts of children, focusing particularly on responses to the major inhalant allergens that have been identified as asthma triggers in later life. The key issues in this context are (1) what factor(s) are responsible for the polarization of allergen-specific helper T cell memory toward the atopy-associated helper T cell type 2 (Th2) cytokine phenotype, and (2) why does the development of this form of helper T cell memory lead to the development of asthma in some but not all individuals with atopic asthma.

WHEN IS THE NAIVE IMMUNE SYSTEM "PRIMED" AGAINST INHALANT ALLERGENS?

Since the initial report by Buckley and colleagues (1), an increasing number of laboratories have independently demonstrated the presence of allergen-specific T cells in cord blood mononuclear cell (CBMC) samples from subjects with and without atopic family history (2–8). The origin of these T cells has until recently been obscure. However, a study involving DNA genotyping of T cell clones derived from allergen-stimulated CBMCs has formally established that these cells are of fetal as opposed to maternal origin (9). Analysis of the cytokine profiles of these allergen-specific fetal T cells has demonstrated universal polarization toward the Th2 cytokine phenotype characterized by production of interleukin 4 (IL-4), IL-5, IL-6, IL-9, IL-10, and IL-13, with a lower and variable contribution from the Th1 cytokine interferon γ (IFN- γ) (9, 10). This unexpected finding appears explicable on the basis of data relating to the immunobiology of pregnancy, which indicate that fetal immune function is strongly Th2 polarized, in order to protect the placenta from the potentially toxic effects of Th1 cytokines such as IFN- γ (11).

The underlying mechanism(s) for this polarization include the constitutive production within the placenta by cells such as trophoblasts of the Th2-trophic cytokines IL-4 and IL-10 (12), together with high-level local production of Th1-inhibitory factors including progesterone and prostaglandin E₂ (13–16). In addition, indirect evidence suggests that the priming process is triggered by transplacental leakage of extremely low levels of allergen from the maternal circulation (6, 8, 17); inhalant allergen has been reported to be present at extremely low levels in the circulation of exposed subjects (18) within the dose range that has been shown experimentally to preferentially prime Th2 immunity (19). It is conceivable that this process may be influenced by transplacentally transferred maternal antibodies

against allergens (6, 20), but definitive proof for such a role is lacking.

THE RELATIONSHIP BETWEEN INTRAUTERINE PRIMING AND SUBSEQUENT ATOPY

It has been suggested that quantitative (2, 8) and/or qualitative (7) differences in this priming process may be associated with predisposition to subsequent atopy development; however, the available supporting data are not convincing. In particular, a prospective study tracking allergen-specific T cell responses between birth and age 2 yr has demonstrated that allergen-induced production of IL-4, IL-6, IL-10, and IL-13 was higher at birth in children who did not express atopy symptoms at the outcome age, in contrast to those who did develop disease (9). Accordingly, more detailed (and longer) prospective studies are required to resolve this important question.

POSTNATAL MODULATION OF FETAL ALLERGEN-SPECIFIC Th2 RESPONSES: WHAT ARE THE ESSENTIAL DIFFERENCES BETWEEN INDIVIDUALS WITH ATOPIC AND NONATOPIC ASTHMA?

Given that the immune system of most children appears "primed" for allergen-specific Th2-polarized immunity, why is subsequent atopy the rule as opposed to the exception? Cross-sectional studies of cohorts of children indicate that by age 5–6 yr, the majority of these fetally primed Th2 responses against inhalant allergens are supplanted by emerging Th1-like responses (21, 22). However, a subset of children appear to consolidate their fetal responses against one or more inhalants and develop skin prick test (SPT) reactivity, and this subset comprises up to 35% of the population. Allergen-specific T cell cytokine production in the SPT⁺ population is dominated by IL-4, IL-5, IL-9, IL-10, and IL-13 together with low IFN- γ (21, 22), consistent with the pattern reported for adults with atopic asthma. There is increasing evidence that these Th2-polarized responses are causally related to the expression of childhood asthma, given the associations reported in this age group between symptoms and the presence of activated Th2 cytokine-producing CD4⁺ cells (23–27) and/or eosinophilia (28, 29).

In contrast, peripheral blood mononuclear cells (PBMCs) from asymptomatic nonatopic children produce only low levels of IFN- γ and IL-10 in response to *in vitro* allergen challenge (21, 22), suggesting that during infancy or early childhood their Th2 response patterns had been redirected via immune deviation.

In support of this suggestion, a prospective study tracking allergen-specific T cell responses from cord blood to age 2 yr has demonstrated age-associated upregulation of IL-4 and IL-13 responses in atopic family history-positive (FH⁺) children who developed atopic symptoms, in contrast to downregulation of the latter in FH[−] asymptomatic children, the latter occurring in conjunction with more rapid postnatal upregulation of allergen-specific IFN- γ responses (30).

Correspondence and requests for reprints should be addressed to P. G. Holt, Ph.D., Division of Cell Biology, TVW Telethon Institute for Child Health Research, P.O. Box 855, West Perth, WA 6872, Australia. E-mail: patrick@ichr.uwa.edu.au.

The postnatal consolidation of these fetal Th2 responses, which is strongly associated with positive atopic family history, may thus be viewed as a failure of this normal immune deviation process.

FAILURE OF IMMUNE DEVIATION PROCESSES IN CHILDREN AT HIGH GENETIC RISK OF ATOPY: A MATURATIONAL DEFECT IN Th1 FUNCTION?

T cell cloning studies contrasting cytokine production patterns in FH⁺ versus FH⁻ infants have demonstrated lower levels of production of both Th1 and Th2 cytokines in FH⁺ subjects, the difference being most marked with respect to the Th1 cytokine IFN- γ (29). This relative deficiency in IFN- γ production during early life in subjects at high risk for atopy has been confirmed in several laboratories studying CBMCs (7, 30–35), and has been suggested to underlie the relatively frequent failure of immune deviation of fetal Th2 responses in infants at risk of atopy (36, 37).

The molecular basis for this defect is unknown. However, it may simply represent the inappropriate postnatal persistence of control mechanism(s) that contribute toward maintenance of the Th2 polarity of immune function during fetal life.

In this context, it is recognized that the principal signal for postnatal upregulation of Th1 function(s) in mammals is microbial stimulation, the most potent source being provided by commensal organisms that rapidly colonize the gastrointestinal tract (GIT) during infancy (36–38). Denial of such stimuli by maintenance of infant animals in a microbial-free environment maintains the Th2 polarity of the immune system that is characteristic of fetal life, such that germ-free animals remain incapable of tolerizing or immune-deviating Th2 responses to mucosally delivered antigens (39). These findings have prompted suggestions that life style-associated variations in postnatal microbial colonization of the GIT in humans may be an important factor underlying the differences in allergy prevalence in first world versus second world pediatric populations (37, 38), and findings from cross-sectional studies of GIT microbial flora in infants in Western versus Eastern Europe have provided initial support for this hypothesis (40, 41). However, more detailed prospective studies are required to determine whether these differences are directly causally related to variations in atopy outcomes.

It is relevant to note in this context that one study has demonstrated a polymorphism in the flanking region of the CD14 gene (encoding the high-affinity receptor for bacterial lipopolysaccharide), which is located on chromosome 5q adjacent to the Th2 cytokine gene cluster, which is associated with the intensity of allergic sensitization within atopic populations (42, 43).

THE ROLE OF ATOPY DEVELOPMENT IN THE SUBSEQUENT EXPRESSION OF ASTHMA: STAGE 1 OF A TWO-STAGE PROCESS?

While it is clear that atopy is a strong risk factor for asthma, it is equally clear that additional cofactors are involved. Thus, while on the order of 40% of children develop SPT sensitivity to ³¹ inhalant allergens in early childhood (22, 44), only a subset of these subsequently develop persistent asthma (44). The immunopathological hallmark of this disease is inflammation of the airway mucosa characterized by the presence of activated Th2 cells, and repeated cycles of allergen-induced Th2-mediated inflammation are hypothesized to lead to phenotypic changes in airway tissues resulting ultimately in the expression of airway hyperreactivity (AHR) (45). The fact that the development of Th2-polarized immunity to inhalants

does not necessarily progress to this second stage infers that the local expression of Th2 immunity in the airway mucosa does not always attain sufficiently high levels of intensity to trigger AHR (46). Consequently, it is likely that additional cofactors including those that modulate the efficiency of local Th2 activation, and/or those that provide additional inflammatory signals within this tissue microenvironment, may play an important role in the disease process (46).

The latter may include viral infections (47), nonallergenic irritants present in house dust (48, 49), and outdoor or indoor air pollutants including environmental tobacco smoke (50–52). The former may include the failure of immunoregulatory mechanisms operative at the level of the airway mucosa, which normally control the intensity and duration of local T cell responses (53). Likely candidates in this group are (1) precocious upregulation of the T cell-activating functions of airway intraepithelial dendritic cell populations, which are normally maintained in an antigen-processing as opposed to antigen presentation mode (54) but which may mature prematurely within these tissues in individuals with atopic asthma (55, 56) as a result of hyperproduction of cytokines such as GM-CSF by adjacent airway epithelial cells (55); (2) excessive local production of NO, which suppresses Th cell activation through effects on phosphorylation of intracellular signaling kinases (57), but which “spares” Th2 cells via differential suppression of Th1 cells (58); and (3) hypoeexpression during inhalant allergen-driven Th2 responses of regulatory cytokines, such as IL-10, that normally provide feedback inhibition of local T cell-mediated inflammation (22, 59). Additional cofactors may also be operative, in particular genetically determined variations in local tissue responsiveness to the inflammatory mediators generated during these responses.

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