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Volume 29 Issue s2



Development of T-cell memory against inhalant allergens: risks for the future

P. G. Holt

Recent evidence suggests that the development of chronic allergic respiratory disease is a biphasic process. Phase 1 commonly occurs during early childhood and in many instances appears to be initiated *in utero*. This involves initial priming of the Th-cell system against ubiquitous environmental allergens, and subsequent reshaping of these responses during infancy into Th1- or Th2-polarized immunological memory. The second phase of the process comprises the repeated expression of Th2-polarized allergen-specific immunity at the level of the airway mucosa, producing cumulative damage to local tissue resulting ultimately in phenotypic changes including development of airways hyperreactivity. It is also clear that this second phase occurs in only a relatively small subset of subjects who develop long-term Th2-polarized allergen-specific immunity, given that the majority of skin prick test positive subjects do not develop chronic airways disease. This suggests that an additional set of control mechanisms, which regulate the intensity/duration of local Th-cell responses within airway mucosal tissues, may play an important role in the ultimate expression of chronic immunoinflammatory disease in the airways in 'at risk' atopic subjects.

Introduction

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It has become evident from recent research that active immunity against common airborne environmental allergens is virtually universal amongst adults, and allergic respiratory disease represents one extreme of a broad spectrum of immune responsiveness against these agents. This conclusion derives from studies that have demonstrated that inhalant allergy is associated with T-cell memory against aeroallergens that are polarized towards the Th2 cytokine phenotype, in contrast to Th1-polarized immunity in nonatopics [1, 2].

It is also clear, however, that Th2-polarized allergen-specific immunity *per se* is not

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sufficient in itself for airway disease development, as only a subset of skin prick test reactive (SPT⁺) subjects develop bronchial hyperreactivity (BHR [3]). Nevertheless, the vast majority of subjects who develop BHR are SPT⁺ to ≥ 1 inhalant allergen [3]. This suggests that factors relating to the intensity of local expression of Th2-dependent inflammation in the airway mucosa may play a major role in airway disease, which awaits definition.

This review focuses upon the early immunological events involved in the development of long-term T-cell memory against airborne allergens, during the preschool years. Of particular interest to this discussion is the issue of whether these early immune responses may be predictive *per se* of airways disease in later life, or whether secondary factors are required.

Intrauterine T-cell priming Go to:

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A brief report in 1992 [4] on the presence of low-level allergen-specific lymphoproliferative reactivity in cord blood mononuclear cells (CBMC), first raised the possibility that initial priming of the developing T-cell system against allergens in the maternal environment may occur *in utero*. Confirmatory reports from several labs (e.g. [5–8]) have substantiated these findings; however, it has been widely debated that the responding cells in CBMC may be of maternal and not fetal origin.

Earlier studies from our group provided indirect evidence supporting fetal origin. Thus, we showed that whereas responses to dietary and inhalant allergens were common in CBMC, responses to the vaccine antigen Tetanus Toxoid (TT) were extremely rare. TT responsiveness was present in the majority of the adult population; also, T-cell responses to the dietary allergen OVA were present in < 20% of adults but were present in the majority of CBMC [8].

More direct evidence has been provided from a recent study in our lab involving cloning of allergen reactive T cells in CBMC and subsequent DNA genotyping; all clones tested were of fetal origin [9]. Preliminary T-cell epitope analysis has also been carried out, and the results suggest recognition of a wide range of epitopes per allergen by CBMC, consistent with the 'immature' nature of these responses [9, 10].

Cross-sectional analysis of allergen-specific cytokine responses in CBMC

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Studies on cytokine production by allergen-stimulated CBMC have been limited by the low precursor frequency of the reactive cells in these immature immune responses; however, employing sensitive sqRT-PCR techniques to measure cytokine-specific mRNA, we have established that these responses are dominated by the Th2 cytokines IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, with less frequent and low-level concomitant IFN γ responses [9, 10]. Certain cytokines, notably IL-6, IL-10, and IL-13, are produced at sufficiently high levels in culture supernatant that they can be readily detected as proteins by enzyme-linked immunosorbent assay [9, 11].

Cell separation and T-cell cloning studies indicate that this IL-10 and IL-13 production in CBMC is from T cells, whereas a major component of the IL-6 is derived from monocytes [9].

The finding of Th2 polarity in these fetal T-cell responses is consistent with the

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Fig. 1 . T-cell immunity to inhalant allergens in relation to age/symptoms.

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emerging literature on the immunology of pregnancy (e.g. see [12]). This indicates that immunological reactivity at the fetomaternal interface is maintained in a Th2 state via the secretion of a range of Th2-trophic and Th1-inhibitory molecules by the placenta, including IL-4 and IL-10 [13], PGE2 [14], and progesterone [15]. The purpose of this polarization is believed to be protection of the placenta against the toxic effects of Th1 cytokines, in particular IFN γ [12].

Analysis of allergen-specific T-cell responses during early childhood

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The findings detailed above are paradoxical in relation to the aetiology of allergic disease, as they imply that at birth it is 'normal' to have an immune system primed for Th2 responses against environmental allergens. Why then is allergy the exception, as opposed to the rule?

On the basis of an earlier series of cross-sectional studies on the relationship between age and lymphoproliferative responses, we suggested the operation of distinct types of regulatory mechanisms for different classes of environmental allergens. Thus, proliferative responses to dietary allergens peaked during infancy, and declined thereafter to very low levels, suggesting negative regulation via the induction of some form of tolerance/unresponsiveness [8]; T-cell epitope mapping of these responses in 5 year olds resulted in comparable conclusions [10].

Cytokine analysis of these dietary allergen-specific responses in 5 year olds revealed only sporadic T-cell-derived IL-13 and IL-10 reactivity, but concomitant high-level IL-6 responses of monocytic as opposed to T-cell origin [16]. Given that low-level IgG production against food allergens is common in both normal and atopic individuals, it is likely that these IL-6 responses may be mediated via IgG-FcR on monocytes. Recent evidence indicates that IL-6 has a variety of anti-inflammatory functions, including stimulation of secretory IgA production [17], antagonism of TNF α and IL-1 [18], and (at high concentrations) inhibition of T-cell activation [19], and its production in the gut wall and associated lymphoid tissues during exposure to food antigens may thus contribute towards the damping of local immune responses to these agents.

These findings contrast strongly with those relating to inhalant allergens. With respect to lymphoproliferation, both the frequency and the intensity of responses increase with age, and by adulthood virtually 100% of the population are reactive to inhalants [8, 10, 20]. Given that T-cell cloning studies have revealed that the underlying cytokine responses to these allergens in adults are compartmentalized into Th1 or Th2 [1, 2] or Th0 [3] phenotypes, from a starting point at birth of low-level Th2 [9], it appears likely that the dominant regulatory mechanism involved is immune deviation (namely low zone tolerance).

Thus, in normal individuals, initial low-level Th2 immunity is converted to Th1 by 5 years of age, whereas the process fails in atopics, leading instead to the consolidation of Th2-polarized inhalant allergen-specific immunological memory involving production of IL-4, IL-5, IL-9, IL-10, and IL-13 [10, 16]. This contrasts with the pattern detailed above for dietary allergen responses, which are reduced markedly by age 5 years, suggesting a form of negative regulation.

As noted earlier [21], the utilization of these different regulatory pathways may be related to the vast disparity between respective levels of exposure to dietary vs inhalant

allergens. This possibility is strongly suggested by the animal literature, indicating that mucosal exposure to high levels of soluble protein antigens leads to anergy and/or deletion of specific T cells, whereas repeated exposure to the same antigens at very low levels instead triggers immune deviation mechanisms [22–24].

Postnatal regulation of inhalant allergen-specific T-cell responses in atopics vs nonatopics: what is the basis for the difference?

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There is increasing interest in the identification of gene polymorphisms that associate with the expression of atopy/asthma, in particular in genes encoding effector molecules that play a role in inflammation. It is becoming clear, however, that these diseases involve multiple genes, and it is likely that different genes play a role at various stages of the disease process.

In relation to the early postnatal period, the key factor in disease pathogenesis is likely to be the efficiency of the immune deviation process, which leads to redirection of fetally primed Th2 responses towards the Th1 phenotype, and recent studies suggest that genetic risk for atopy/asthma is associated with lowered capacity to generate the principal Th1 cytokine IFN γ during this life phase.

This conclusion stems initially from studies in our laboratory on T-cell cloning in infants with/without atopic family history [25], and is reinforced by the results of a series of comparative studies on IFN γ production by PHA-stimulated CBMC from family history positive/negative donors [26–29].

Recent reports on responses to vaccination in infants also suggest compromised Th1-dependent immune function in association with susceptibility to atopy/asthma. Thus, a retrospective study on 12-year-old Japanese children indicated that atopy/asthma at age 12 was markedly more frequent in children who had previously failed to generate long-term Th1-dependent immunological memory against BCG vaccination during infancy, than in those who responded fully to vaccination [30]. We have also recently reported that *in vitro* T-cell responsiveness to Tetanus vaccination in 2 year olds is inversely related to total serum IgE levels [31].

It should be noted in this context that capacity to express Th1-associated functions such as IFN γ production is reduced in all children relative to adults, and does not 'mature' until approximately age 5 years [32]. Given that no gross differences between atopic and normal adults have been identified at the polyclonal T-cell level with respect to IFN γ production, the disparity noted above between atopic family history positive/negative children is thus likely to represent a transient maturational defect, i.e. a temporal delay in the transition from the fetal Th2-polarized to the Th1-polarized cytokine phenotype characteristic of adults. We hypothesize that at the population level, this delay is associated with a higher frequency of 'failures' in the immune deviation process, which normally silences fetally primed Th2-dependent immune responses.

Allergen-specific T-cell immunity vs expression of symptoms

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The scheme depicted in Fig. 1 attempts to place the *in vitro* findings on the development of allergen-specific T-cell memory in context with relevant epidemiological findings

related to airway disease. Thus, the T-cell system is weakly 'primed' *in utero*, and as a result of the production of a range of Th2-trophic/Th1 inhibitory molecules at the fetomaternal interface, these responses are Th2-polarized. After birth, direct environmental exposure to higher levels of allergens occurs, and these fetomaternal influences wane as the infant immune system matures; the developing allergen-specific T-cell responses are accordingly subjected to a variety of selection pressures, resulting in either boosting of pre-existing Th2 responses or their immune deviation towards the Th1 cytokine phenotype. Figures from both epidemiological and *in vitro* studies indicate that by age 5 years, $\approx 60\%$ of children have successfully deviated their fetal Th2 responses to Th1, whereas $\approx 40\%$ of children are SPT⁺/Th2⁺ to ≥ 1 inhalant allergen.

As noted above, however, only a subset (one-quarter to one-third) of the SPT⁺ appear destined to develop chronic BHR, the remainder expressing symptoms in other tissues or remaining essentially asymptomatic.

The available information on the immunohistopathology of airway mucosal tissue samples from BHR⁺ subjects suggests that the 'black box' in [Fig. 1](#), which leads to BHR, is chronic inflammation, i.e. repeated cycles of tissue damage and subsequent remodelling, driven by Th2-dependent responses to inhaled allergens to which the subject is sensitized.

But why is this restricted to only a subset of Th2⁺/SPT⁺ subjects, whereas the degree of local tissue damage in the remainder does not exceed the threshold required to trigger development of BHR?

Regulation of the intensity of
Th2-driven
immunoinflammatory responses
in airway mucosal tissues:
endogenous vs exogenous
factors

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(i) Exogenous factors. One possible scenario is that allergen-specific Th2 responses are generally of insufficient intensity to trigger BHR in their own right, but can do so in combination with other pro-inflammatory environmental factors. These factors include air pollution [[33](#)], but perhaps more importantly viral infection [[34](#), [35](#)].

(ii) Endogenous factors. The second possibility [which may act in combination with (i) above] is that endogenous control mechanisms that normally limit the intensity and duration of T-cell-dependent inflammatory responses in the airway mucosa, may fail in atopics, resulting in enhanced local inflammation.

The nature of these mechanisms are not fully understood, but recent research has highlighted several pathways that may be important in airway disease. One of the most likely of these involves the functional maturation of airway mucosal dendritic cells (DC), which are now recognized as the principal resident antigen-presenting cell population in resting airway tissue [[36](#), [37](#)], and also as a major cellular element in the host response to acute and chronic airways inflammation [[38–41](#)]. Under normal conditions, these DC are specialized for the uptake and processing of antigen but are unable to present antigen-specific activation signals to T-cells, a function that only develops in response to cytokine signals the DC receive after migration to regional lymph nodes. The principal cytokine signal involved is GM-CSF, however, which is readily produced by a variety of cells within the inflamed airway mucosa, including by airway epithelial cells [[42](#)].

Other control mechanisms operate to limit the capacity of airway DC to respond locally to GM-CSF and hence upregulate their antigen-presenting cell functions. The most potent of these appears to be nitric oxide (NO). Macrophage-derived NO is an effective inhibitor of GM-CSF-mediated upregulation of DC functions [43]. NO is produced in high levels by airway epithelial cells in inflammation [44], and this may also function to limit DC activity. Pulmonary alveolar macrophages are extremely potent in this regard, and interference with their *in vivo* functions in experimental animals has been demonstrated to lead to rapid upregulation of lung DC activity [43] and to markedly increase responsiveness to inhaled antigens [45, 46]. Additionally, pulmonary alveolar macrophages have been shown to directly inhibit T-cell activation, a process in experimental animals that is again attributable to NO [47, 48]. It is also of interest to note that cytokines such as the combination of GM-CSF and TNF α , and TGF β alone, which are commonly produced early in inflammatory responses in the lung, have been demonstrated to inhibit the capacity of lung macrophages to produce NO [49, 50]; this provides a further mechanism for fine-tuning these T-cell regulatory processes during the course of immunoinflammatory responses.

Our recent studies indicate that NO interferes with T-cell activation via inhibition of intracellular signalling kinases such as Jak3/STAT 5 [51]. This process permits partial activation of T-cells and their cytokine secretion, but inhibits their local clonal expansion; iNOS activation within airway epithelial cells may thus be part of a 'self protection' loop, the principal purpose of which is to limit the intensity and duration of intraepithelial T-cell responses.

Conclusions

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On the basis of recently available information it seems reasonable to suggest that the development of atopic respiratory disease can be divided broadly into two stages, comprising (i) an inductive phase, during which allergen-specific T-cell memory develops and is compartmentalized into the Th2-polarized cytokine profile, and (ii) the expression phase, involving a breakdown of endogenous cellular control mechanisms that normally regulate the intensity and duration of immunoinflammatory responses within airway mucosal tissues, resulting in chronic Th2-driven inflammation in the bronchial mucosa culminating in BHR development.

It is tempting to speculate that (ii) may be a common factor in both allergic respiratory disease and chronic obstructive pulmonary disease.

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