

The Role of Airway Dendritic Cell Populations in Regulation of T-Cell Responses to Inhaled Antigens: Atopic Asthma as a Paradigm

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ABSTRACT

Chronic atopic asthma in adulthood represents the end stage of a disease process that is initiated during the perinatal period, when the naive immune system is first confronted with potentially allergenic airborne antigens. The initial phase involves compartmentalization of immunological memory into either the T-helper (Th)–1 or Th2 cytokine phenotypes, in atopic and nonatopics, respectively, and in a subset of atopics, this results in chronic Th2 cytokine-driven inflammation in the airways. Dendritic cells appear to play a key role in directing the memory generation process, and in subsequently controlling the intensity and duration of the ensuing Th-cell responses responsible for this inflammation.

Key words: dendritic cells, respiratory tract, T-cells, cytokines

INTRODUCTION

THE CHARACTERISTIC AIRWAYS pathology of atopic asthma is the end result of repeated cycles of inflammation-induced tissue damage, driven by the local activation of allergen-responsive T-cells. This brief review will focus upon the principal cell populations that initiate this process, CD4⁺ Th2-memory cells, and respiratory tract dendritic cells (RTDC), which are the principal antigen presenting cells (APC) in the airway wall and thus control local T-cell activation. The discussion on CD4⁺ T-cells concentrates primarily upon the nature of the cytokine phenotype of Th-memory cells in atopics, and will examine the process that results in programming of immunological memory, whereas discussion of RTDC will focus on their functional phenotype *in situ* and how dys-

regulation of these functions may influence the pathogenesis of chronic inflammation diseases in the airways.

ALLERGEN-SPECIFIC IMMUNITY IN ATOPIC AND NONATOPIC ADULTS

Th1/Th2 paradigm was first described in murine systems by Mossman and colleagues.¹ During the early 1990s, this was extended to human atopy, with the demonstration that reciprocal patterns of CD4⁺ Th-memory distinguished allergen sensitized responders (Th2-like) from nonatopic clinically unresponsive subjects (Th1-like^{2–4}). More recent information suggests that, while the production of Th2 cytokines such as IL-4, IL-5, IL-9, and IL-13 is indeed a hallmark char-

acteristic of skin prick test positive (SPT⁺) atopics, these subjects also commonly produce the Th1 cytokine IFN γ .^{5,6} and hence their responses may be more accurately described as Th0-like by analogy with the mixed cytokine pattern observed in chronically stimulated murine Th-memory cells.⁷

The classification of these patterns of immunity in atopics and nonatopics is a subject of continuing controversy, as increasing evidence accumulates on the heterogeneity of cytokine response patterns in different patient groups. For example, while there is general acceptance that T-cells secreting Th2 cytokines, particularly in combination with eosinophils, play a key role in airways inflammation in atopic asthma,^{8,9} the designation of allergen-specific T-cell immunity in nonatopics as "Th1-like" is not universally accepted on the basis that these subjects show no evidence of delayed hypersensitivity.¹⁰ Paradoxically, it has also been shown that the airways of nonatopic asthmatics contain infiltrates of eosinophils and Th2 cells.^{11,12} It has also been reported that, with some inhalant allergens, clinical unresponsiveness is associated with development of a pattern of T-cell immunity, which is permissive for ongoing production of Th2-dependent IgG4 antibody but not IgE.¹³ It has been suggested that this latter finding is inconsistent with the murine Th1/2 model in which cross-regulation between mutually antagonistic populations of T-cells is held to be a central mechanism. An alternative interpretation is that there is nothing inherent in the Th1/2 model which mandates that polarization of Th-memory responses must be absolute; instead, it is assumed that cross-regulation results in the establishment of an equilibrium in which one Th-cell type is dominant, and the mixed nature of allergen-specific Th-cell responses in many atopics^{5,6} is consistent with this notion. Also, cross-inhibition of the production of Th2-dependent antibodies by IFN γ cannot be described by a single dose response curve, as IgE secretion by human PBMC is completely inhibited by IFN γ concentrations at which significant levels of IgG4 production still occur.^{14,15}

It should also be noted that, in earlier studies employing an experimental rat/mouse model in which "tolerance" to allergen is induced by repeated exposure to the allergen in aerosol form,^{16,17} we have demonstrated that IgE antibody synthesis is preferentially sensitive to suppression relative to IgG antibody production, which persists for long periods. This type of ac-

quired response pattern is known as "split tolerance," the underlying mechanisms of which remain to be determined. It is additionally noteworthy that earlier studies have demonstrated that this form of tolerance can be adoptively transferred in the rat/mouse model employing IFN γ -secreting T-cells,^{18,19} and more recent studies have implicated IL-10-secreting T-regulatory cells in this process.²⁰

Ongoing studies in our lab are developing a new approach to this issue, involving assessment of the activity of genes encoding regulatory proteins that act upstream of cytokine genes, in particular, transcription factors (TFs). The impetus for these studies is provided by recent murine experiments that point to an important role for TFs such as GATA-3 in driving the differentiation of naive CD4⁺ Th-cells towards expression of the Th2 cytokine phenotype.

We initially tested the applicability of these findings to humans in a study on naive CD4⁺ Th-cells, which demonstrated that IL-4-driven Th2 differentiation is associated with upregulation of GATA-3 expression, whereas a reciprocal pattern (downregulation) accompanies Th1 differentiation. More importantly, these GATA-3 expression patterns are mirrored in allergen-specific responses of mature CD4⁺ Th-memory cells. In particular, overnight culture of PBMC from IgE-producing HDM-sensitive subjects in the presence of HDM results in upregulation of GATA-3 expression, in contrast to downregulation in nonatopic subjects.²¹ These data have recently been validated employing quantitative real-time PCR. These findings provide confirmatory evidence of (a) cognate immunity against environmental allergen by nonatopics, and (b) dichotomous patterns of immunity in atopics/nonatopics, employing a measure of T-cell activation that is not subject to the vagaries of long-term proliferation assays or ELISAs.

PRIMING THE T-CELL SYSTEM AGAINST ALLERGENS DURING CHILDHOOD AND THE DEVELOPMENT OF LONG-TERM IMMUNOLOGICAL MEMORY

Over the last decade, many laboratories have reported the presence of allergen-specific CD4⁺ Th-cells in cord blood,²² and we have formally demonstrated the fetal origin of these T-cells.²³ This suggests that airborne allergens inhaled by

the mother during pregnancy, or possibly cross-reacting antigens from other sources, are transported across the placenta at levels sufficient to initiate T-cell priming.

These early T-cell responses as measured in bulk CBMC cultures are dominated by Th2 cytokines, but T-cell clones derived from these cultures also produce IFN γ .²³ The majority of these responses appear to be progressively redirected ("immune deviated") towards a Th1-like pattern during early childhood, comprising low-level production of IL-10 and IFN γ .^{24,25} A subset of responses in a minority of children consolidate their Th2-like pattern, and the frequency with which this occurs is highest in children who are atopic family history positive (AFH⁺^{24,25}).

We have previously demonstrated²⁶ that AFH⁺ infants who are genetically at high risk (HR) of atopy display lower levels of Th1 competence (as measured by capacity to produce IFN γ in response to polyclonal stimuli) relative to their LR (AFH⁻) counterparts, and these observations have been extended to cord blood.^{27,28} The constitutive "Th2 bias," which is the hallmark of the fetal immune system,²⁹ is more marked in AFH⁺ subjects, and the kinetics of postnatal maturation of Th1 function is slower in these children. We hypothesize that this results in reduced capacity to develop the low-level Th1-like form of allergen-specific CD4⁺ Th-memory characteristic of non-atopics, thus increasing the probability of consolidation of these responses into the reciprocal Th2-like pattern.^{27,28}

It is likely that several mechanisms underlie these differences in susceptibility to development of Th2-polarized memory to inhaled allergens in AFH⁻ versus AFH⁺ children. Firstly, earlier studies on human neonatal APC function²⁷ and more recent work in the mouse³⁰ indicate that delayed maturation of these cells contributes to the reduced expression of Th1 immunity during early postnatal life. Secondly, it is recognized that one of the primary signals for postnatal development of Th1 competence in mammals is provided by microbial stimulation, including commensal bacteria in the GIT,^{31,32} and genetically determined variations in the function of the major receptor for microbial signalling (CD14) appears to be an important contributory factor.³³ Ongoing studies in our laboratory are also addressing more fundamental downregulatory mechanisms operative at the level of the promoter of the IFN γ gene, notably cytosine methylation in the context of CpG motifs, which modulate accessibility to

key TFs required for initiation of gene transcription. Our findings indicate that levels of CpG methylation are much higher in naive neonatal CD4⁺ T-cells relative to naive adult CD4⁺ T-cells, consistent with relative suppression of the fetal IFN γ gene.

Whatever the key Th1-regulatory mechanisms operative in early life prove to be, they clearly influence a range of immunological processes in addition to atopy. In particular, expression of the atopic phenotype is associated with diminished capacity to develop stable Th-memory to the Diphtheria-Tetanus-Pertussis vaccine during early infancy,^{34,35} and also responsiveness to pneumococcal polysaccharide vaccine³⁶ and BCG.^{27,37} Additionally, low Th1 competence in cord blood cells (as measured by IL-12 or IFN γ production) has been associated with increased risk for subsequent RSV infection and, in particular, risk for development of bronchiolitis accompanying infection, presumably reflecting a diminished capacity to prevent the downward spread of infection to the lower airways.^{35,38,39} These findings suggest the intriguing possibility that susceptibility to RSV wheeze and atopic asthma may be programmed by the same family of genes.⁴⁰

We have recently integrated these findings into an overall model for the natural history of atopic asthma.^{28,40} The central features of the model are as follows:

1. Initial priming of CD4⁺ Th-cell responses to airborne allergens, which occurs during early life against a background of developmentally directed Th2 polarization within the immature immune system
2. Subsequent modulation of these responses via allergen-driven Th-cell-mediated cross-regulation, resulting in stable Th0/Th2-like or Th1-like memory expression by the end of the preschool years
3. Progression of allergic sensitization to persistent asthma in a subset of atopics (<25%⁴¹), being most frequent in those who are sensitized in early postnatal life,^{42,43} and, in particular, in those atopics who develop wheeze in infancy in response to infection⁴⁴
4. It has been suggested that in this latter subgroup, damage to airways during critical stages of lung growth via a combination of allergy and infections may influence the differentiation and subsequent functions of the lung, resulting in development of persistent airways hyperresponsiveness^{45,46}

REGULATION OF THE INDUCTION AND EXPRESSION OF T-CELL IMMUNITY IN THE AIRWAYS: THE KEY ROLE OF RTDC IN CONTROLLING LOCAL IMMUNOLOGICAL HOMEOSTASIS IN THE STEADY STATE

The distinguishing hallmark of the subset of atopics who develop persistent asthma is excessive levels of Th-activation in the airway mucosa.⁴⁷ This suggests an important role for local APC in diseases pathogenesis, in particular RTDC,⁴⁹ which is the most important APC population in these tissues. These RTDC also play a major role in setting the Th1/Th2 balance in immune responses to all classes of inhaled antigens. We have recently demonstrated in rat studies that RTDC constitutively drive these responses towards the Th2 phenotype unless appropriate Th1-inductive signals are received from their microenvironment,⁴⁹ and similar findings have been reported in mice.⁵⁰ These findings provide a plausible explanation for the role these RTDC play in the mouse model of asthma, in the induction of local airway eosinophilia.⁵¹ Additionally, it is likely that the cells of this RTDC network are responsible for presentation of the inhalant allergen signals to the T-cell system in early postnatal life, which drive Th1/Th2 cross-regulation during allergen-specific Th-memory development.

It is clear that, in experimental animals, these RTDC networks are numerically sparse and functionally deficient during infancy, and do not develop to resemble the mature adult pattern until after biological weaning.^{52,53} Elucidation of their ontogeny in humans is thus a key issue in relation to the etiology of inhalant allergy. Recent studies on postmortem samples suggest that the kinetics of postnatal development of the DC network in the large conducting airways in humans may be similar to that in rodents,⁵⁴ but no accompanying functional data are available.

RTDC FUNCTIONS IN INFLAMED AIRWAY TISSUE

In immunocompetent adult rats, local inflammatory challenge of the airways leads to rapid upregulation of RTDC networks,^{55–57} markedly accelerating an already rapid turnover rate.⁵⁸ We have recently demonstrated that upregulation of

this network, involving increased rates of migration of DC precursors into airway tissues and accompanying increased traffic to regional lymph nodes, occurs in response to virtually all classes of antigens.⁵⁹ Our most recent studies⁶⁰ indicate that the RTDC employ different chemokine programs as a function of the nature of the eliciting stimulus, thus maintaining maximum flexibility in relation to optimising their capacity to deal with a wide range of environmental challenges.

There is increasing evidence that RTDC networks in human airway mucosal tissues have a comparable capacity for responsiveness to external stimuli, the prime example being atopic asthma in which these cells are present in increased numbers, and they express a variety of surrogate markers of activation.^{61–63}

We have recently obtained the first direct evidence, employing serial bronchial biopsies, that DC in human atopic asthmatics are rapidly recruited into the bronchial mucosa during the acute phase of the response to local allergen challenge.⁶⁴ Moreover, baseline levels of RTDC are reduced in steroid-treated atopics, and recruitment is also attenuated by these drugs,⁶⁴ confirming earlier observations in the rat model.⁶⁵ It is pertinent to note that no CD123⁺ plasmacytoid DC were observed in these bronchial biopsies, whereas this DC subset is prominent in the human nasal mucosa of subjects with allergic rhinitis,⁶⁶ suggesting potentially different mechanisms of T-cell regulation in these two areas within the respiratory tract.

REGULATION OF THE FUNCTIONAL PHENOTYPE OF RTDC *IN SITU*

One of the most important findings in this area has been the consistent demonstration that in the steady state, resident RTDC do not express the full array of costimulators and/or other function-associated molecules, which are required to enable them to efficiently present antigen to T-cells.⁶⁷ This finding was originally made in rats, and subsequently has been verified in studies in other species, providing the researchers employed rapid DC preparative methods that avoid *in vitro* activation of the cells.⁴⁸ Their function in the steady state is thus a "sentinel cell" specialized for efficient uptake of antigen and transport to regional lymph nodes.⁴⁹ During migration or upon arrival in the lymph node, they receive ac-

tivation/maturation signals that induce their final functional maturation into potent APC.^{49,68} One of the most important activation signals for RTDC is the cytokine GM-CSF, which is produced constitutively at low levels by airway epithelial cells.

We have demonstrated that, in normal animals, RTDC are prevented from responding *in situ* to the activating effects of GM-CSF by NO produced by local tissue macrophages,⁶⁸ and further that selective elimination of pulmonary alveolar macrophage populations *in vivo* via intratracheal administration of macrophage-cytocidal drugs in liposomes renders both rats⁶⁹ and mice⁷⁰ hyperresponsive to inhaled antigens. This suggests that environmental agents capable of inhibiting NO production by lung macrophages (possibly certain air pollutants and viruses) may interfere with this regulatory mechanism, permitting precocious *in situ* functional maturation of RTDC, which could in turn lead to local inflammation resulting from local release of cytokines from T-cells activated by the functional DC.

An experimental model demonstrating the potential for such mechanism has recently been developed by Jordana and colleagues⁷¹ involving targeted GM-CSF transgene hyperexpression in the airway of mice, which rendered them susceptible to allergic sensitization to inhaled allergen. Hyperproduction of GM-CSF by damaged airway epithelial cells has been demonstrated in atopic asthmatics,⁷² and airway DC in this disease reportedly express at least some markers of activation,⁶² suggesting a possible role in amplification of local Th2-cell mediated inflammation.

UNRESOLVED ISSUES

Despite these tantalizing hints of the potential importance of local RTDC activation in the pathogenesis of local airways inflammation, direct evidence of such an occurrence in an experimental model involving the use of realistic environmental stimuli is still lacking. Ongoing studies in our lab are focusing upon this issue at present, in particular on recall responses of primed animals to OVA aerosols, and in animals exposed to aerosolized bacterial extracts. We have preliminary evidence of transient upregulation of CD80/CD86 expression (the costimulator that is "limiting" in relation to expression of APC activity by RTDC) during a brief time-window post-

exposure, but as yet have not demonstrated that such cells can productively interact with T-memory cells *in situ* in the airways.

Likewise in asthma, while it is clear that the RTDC network expands in the face of either acute or chronic allergen exposure, definitive evidence of local functional maturation is still lacking, in this or any other inflammatory airway disease.

More importantly, information is still lacking on the relative contributions of DC subpopulations derived from lymphoid versus myeloid precursors, in local immune regulation. Given recent developments in other areas of the immunological literature indicating the wide range of functions that can be performed by these different cell types, this represents a question of major importance to our understanding of how immune responses are regulated in the lung and airways. These and other issues await further research.

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