

Human Th1 and Th2 lymphocytes: their role in the pathophysiology of atopy

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In human beings, as in mice, two distinct patterns of cytokine secretion have been defined among CD4 + helper T-cell clones. Human type 1 helper (Th1), but not type 2 helper (Th2), cells produce interleukin-2 (IL-2), gamma-interferon (IFN- γ), and tumor necrosis factor- β , whereas Th2, but not Th1, cells secrete IL-4 and IL-5, but not IL-2 or IFN- γ . Other cytokines, such as IL-3, IL-6, GM-CSF, or TNF- α , are produced by both Th1 and Th2 cells. Th0 cells, a third Th subset, show combined production of Th1- and Th2-type cytokines. The different cytokine patterns are associated with different functions. In general, Th2 cells provide an excellent helper function for B-cell antibody production, particularly of the IgE class. On the other hand, Th1 cells are responsible for delayed type hypersensitivity reactions and are cytolytic for autologous antigen-presenting cells, including B cells. Most allergen- or helminth-antigen-specific human CD4 + T-cell clones exhibit a Th2 phenotype, whereas most clones specific for bacterial antigens show a Th1 profile. Allergen-specific Th2 cells seem to play a crucial role in atopy. These cells induce IgE production via IL-4 and favor the proliferation, differentiation, and activation of eosinophils via IL-5. In addition, Th2-derived IL-3 and IL-4 are mast-cell growth factors that act in synergy, at least *in vitro*. Recent evidence indicates that allergen-specific Th2 cells are selectively enriched in tissues affected by allergic inflammation, such as the bronchial mucosa of subjects with allergic asthma. However, the reason why allergens preferentially expand Th2 cells in atopics is unknown. A number of factors may influence Th subset differentiation into Th1 or Th2 cells. At present, the IL-4 produced in the microenvironment in which antigen is presented to Th cells seems to be the major factor favoring Th2 development. In this connection, the aberrant production of IL-4 (and IL-5) exhibited by T cells from atopics, even in response to bacterial antigens, may be of great importance.

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Introduction

The interaction between environmental allergens and the immune system is critical to the development of human allergy. This interaction is presumably initiated by uptake and presentation of allergens by MHC class II positive accessory cells to helper T (Th) cells. Activated Th cells then induce B cells to produce allergen-specific antibodies, mainly those belonging to the IgE class. However, the origin of the preferential expression of IgE isotype in allergen-specific antibody production in individuals genetically determined to recognize allergen epitopes is still unclear. In the last few years, a pathway of IgE

regulation, essentially based on the reciprocal activity of interleukin-4 (IL-4) and gamma-interferon (IFN- γ), has been discovered in mice (5).

Two very distinct patterns of cytokine secretion were defined among a series of mouse CD4 + T-cell clones (25). Upon stimulation, type 1 (Th1), but not type 2 (Th2), T helper cells produce IL-2, IFN- γ , and TNF- β , whereas Th2, but not Th1, cells secrete IL-4, IL-5, IL-6, and IL-10 (27). Other cytokines, such as TNF- α , IL-3, and GM-CSF, are produced by both Th subsets. The different cytokine profiles are associated with very distinct functions of the two types of T cells (reviewed in 17, 26). In general, Th2 clones express an excellent helper function for B-cell

immunoglobulin (Ig) secretion, particularly of the IgE class (3). Under some circumstances, Th1 clones can also provide help to B cells, but one of their major functions is to induce delayed type hypersensitivity (DTH) reactions (3). Other phenotypes of cytokine secretion have been described in mouse Th clones. A pattern characterized by the concomitant production of IL-2, IFN- γ , IL-4, and IL-5 has been coded as Th0 (14, 37).

In a number of immune responses, there is a reciprocal interaction between DTH and humoral responses. If these two types of immune response approximately correspond to the preferential activation of Th1 and Th2 cells, respectively, this reciprocal relationship could be due to mutual inhibition by Th1 and Th2 cells. Indeed, IFN- γ produced by Th1 inhibits the growth of Th2 cells (14), whereas IL-10 produced by Th2 inhibits the cytokine synthesis by Th1 clones (13).

It has been suggested that the different functional Th subsets in the mouse arise post-typically from a common pool of precursors, and as a consequence of activation by antigens (38–40, 42). This concept raises the question of the factors able to induce the two differentiation pathways. The most convincing examples of such factors are IFN- γ and IL-4. IFN- γ promotes the differentiation of precursors into Th1 cells, both *in vitro* (15) and *in vivo* (6, 20, 36), whereas IL-4 has the reciprocal activity of inducing differentiation into Th2 both *in vitro* (40) and *in vivo* (6, 20). There are a number of other possible factors that may influence Th subset differentiation. They include MHC genotype (28), antigen epitopes (19), antigen-presenting cells and their costimulatory signals (43), quantitative differences in T-cell activation (2), and locally active hormones (7).

Human Th1 and Th2 cell subsets

Initial studies of panels of mitogen-induced or alloreactive T-cell clones derived from the peripheral blood of healthy donors suggested that most human CD4⁺ Th cells cannot be divided into clear-cut Th1 or Th2 subsets (22, 29). However, CD4⁺ Th cells with definite Th1 or Th2 phenotypes could be isolated from the peripheral blood or tissues of patients with different diseases. Most of the CD4⁺ T-cell clones derived from thyroid lymphocytic infiltrates of patients with thyroid autoimmune diseases showed a definite Th1-like profile of cytokine secretion when stimulated by mitogens (9). A series of host-reactive CD4⁺ T-cell clones, isolated from a patient with severe combined immunodeficiency with a transplant, showed a selective defect of IL-4 production (1). Conversely, a severe defect of Th1-like CD4⁺ T cells was found in patients with hyper-IgE syndrome (10). Furthermore, higher proportions of Th2-

like and lower proportions of Th1-like T-cell clones were isolated in our laboratory from the peripheral blood of patients with severe atopic disorders or helminth infections, such as toxocariasis or filariasis, than in healthy controls (33).

Expansion of the Th2-like cell subset in patients with deregulated IgE production

The findings reported above have encouraged investigations into whether alterations of the proportions of Th1- and Th2-like cells are involved in the genesis of human diseases characterized by hyperproduction of IgE.

Patients with helminthic infections or atopic disorders usually exhibit both elevated serum IgE and eosinophilia. Since IL-4 is essential for B-cell differentiation into IgE-producing cells (5, 8, 25) and promotes mast-cell growth (34), and since IL-5 promotes differentiation (4, 35), vascular adhesion (41), and *in vitro* survival of eosinophils (21), it is reasonable to suggest that Th cells resembling the Th2 murine subset in their ability to produce IL-4 and IL-5, but not IFN- γ , may play a role in atopy and immune response to helminths.

In subsequent studies, mitogen-induced T-cell clones derived from the conjunctival infiltrates of patients with vernal conjunctivitis (VC) were examined. The great majority of clones obtained from VC infiltrates were CD4⁺ T cells that could be induced to produce high concentrations of IL-4 and that could provide helper function for IgE synthesis by B cells. In contrast, even after maximal stimulation, such as that delivered by the phorbol ester PMA plus anti-CD3 antibody, only a few clones expressed IFN- γ mRNA and could produce IFN- γ (23). Taken together, these data suggest that in atopic patients both production of IgE and eosinophilia probably result from the expansion of Th2-like cells and/or their preferential accumulation in target organs.

Different antigens can expand helper T-cell subsets with Th1 or Th2 phenotypes of cytokine secretion

In order to provide additional information on the nature of the Th2-like cells found in patients with helminthiasis or allergic disorders, as well as on the mechanisms responsible for their development, our strategy has been to establish T-cell clones specific for allergens (house-dust mite and Rye I), helminthic components (excretory/secretory antigen of *Toxocara canis* – TES), or bacterial components (such as purified protein derivative [PPD] of *M. tuberculosis*). This approach was based on the observation that, although toxocariasis is quite rare, there is frequent exposure to *T. canis*, as demonstrated by the high

prevalence of *in vitro* lymphoproliferative response to TES antigen in the general population. The choice of PPD was based on the observation that, unlike helminth infection and allergy, infection with *M. tuberculosis* usually results in delayed type hypersensitivity reactions, but not production of IgE and eosinophilia.

When high numbers of T-cell clones specific for PPD or TES antigen derived from healthy individuals were compared, a stable and clear-cut dichotomy in the profile of cytokine secretion was observed. Virtually all PPD-specific clones produced IL-2 and IFN- γ , but not IL-4 and IL-5 (Th1-like), whereas the great majority of TES-specific clones produced IL-4 and IL-5, but not IL-2 and IFN- γ (Th2-like) (11). Th1-like, but not Th2-like, clones produced TNF- β , whereas both types of clones produced variable amounts of TNF- α , IL-3, IL-6, and GM-CSF (Table 1). As expected, Th2 TES-specific clones consistently supported IgE synthesis by autologous B cells under MHC-restricted conditions, whereas Th1 PPD-specific clones did not. These results demonstrate that PPD and TES antigens selectively expand helper T cells with stable and opposite (Th1 or Th2) phenotypes of cytokine secretion.

More recent studies have shown that human Th1 and Th2 clones differ not only in their pattern of cytokine secretion, but also in their cytotoxic capacity and their mode of helper function for Ig synthesis. In fact, the great majority of Th1, but only a minority of Th2, clones exhibited cytolytic activity. In addition, all Th2 (noncytolytic) clones induced IgM, IgG, IgA, and IgE synthesis by autologous B

cells in the presence of the specific antigen, and the degree of response was proportional to the number of Th2 cells added to B cells. Under the same experimental conditions, Th1 (cytolytic) clones provided a helper function for IgM, IgG, and IgA, but not IgE, synthesis with a peak response at 1:1 T:B cell ratio, but at higher T:B cell ratios a strong decrease of Ig synthesis was observed (12). The decrease of Ig production at high Th1:B cell ratios directly correlated with the degree of lytic activity of Th1 clones against autologous antigen-presenting B cells (12).

Allergen-specific T-cell clones derived from atopic subjects usually exhibit a Th2 profile of cytokine secretion

High numbers of T-cell clones specific for the house-dust mite *Dermatophagoides pteronyssinus* (DP) or grass-pollen Rye I could be obtained from mite- or grass-sensitive atopic subjects. Most allergen-specific clones produced IL-4 (and IL-5) in response to mitogen stimulation, and a proportion of them (37%) failed to produce IFN- γ . When stimulated with the specific allergen under MHC-restricted conditions, the great majority of allergen-specific T-cell clones behaved like Th2 cells (30). These data support the view that in individuals genetically determined to recognize allergen epitopes (24), immune response to environmental allergens results in the preferential activation of Th2 clones. These cells help both to produce IgE antibodies and to increase the number of eosinophils through their release of IL-4 and IL-5, respectively.

More recently, we asked whether inhalation of clinically relevant allergens might result in the activation of allergen-specific CD4⁺ T cells in the bronchial mucosa of patients with atopic asthma. To answer this question, we obtained T-cell clones from endobronchial biopsies taken 48 h after a positive bronchoprovocation test with grass-pollen extract from atopic patients with grass-pollen-induced atopic asthma and compared them for both phenotype and functions with T-cell clones derived from endobronchial biopsies taken 48 h after a positive bronchoprovocation test with toluene diisocyanate (TDI) from nonatopic patients with TDI-induced asthma. Most clones derived from atopic patients were CD4⁺, whereas most clones derived from patients with TDI-induced asthma were CD8⁺. Upon mitogen stimulation, 40% of CD4⁺ clones from atopics, but 17% of CD4⁺ clones from nonatopic asthmatic patients, exhibited a Th2 pattern of cytokine secretion. Interestingly, a proportion of CD4⁺ T-cell clones derived from atopic patients, but none of those derived from nonatopic asthmatics, showed both proliferation and cytokine production in re-

Table 1. Functional properties of CD4⁺ human T helper cells

	Th1	Th2	Th0
Cytokine secretion			
IL-2	+++	-	+++
IFN- γ	+++	-	+++
TNF- β	+++	-	+
IL-4	-	+++	+
IL-5	-	+++	+
IL-3	+	++	+
IL-6	+	++	+
GM-CSF	+	++	+
TNF- α	+++	+	++
Helper function for Ig synthesis			
IgE	-	+++	+/-
IgM, IgG, IgA			
low T:B cell ratio	++	++	++
high T:B cell ratio	-	+++	+/-
Cytolytic activity	+++	+/-	++
Need for development	IFN- γ	IL-4	?
Proliferation and cytokine production in response to:			
IL-2	↑	↑	↑
IFN- γ	==	↓	?
IL-4	==	↑	?
IL-10	↓	↓	↓

sponse to grass-pollen allergens under MHC-restricted conditions. The great majority of them exhibited a clear-cut Th2 profile and induced the synthesis of IgE in autologous B cells in the presence of the specific allergen (Del Prete et al., submitted).

These data suggest that, because of their pattern of cytokine production, allergen-specific Th2 cells are responsible for induction of both allergen-specific IgE (via IL-4) and eosinophilia (via IL-5) and therefore play a central role in determining the nature of the inflammatory response seen in the bronchial mucosa of asthmatic atopic patients. This possibility is supported by recent evidence demonstrating positive signals for IL-5 and IL-4, but not IFN- γ , mRNA in allergen-induced, late-phase cutaneous reactions (18) in bronchial biopsy specimens (16), and in bronchoalveolar lavage fluid (32) of patients with atopic asthma.

Aberrant IL-4 and IL-5 production *in vitro* by CD4⁺ helper T cells from atopic subjects

Additional knowledge emerged when the phenotypes of cytokine secretion of a high number of PPD- and tetanus toxoid (TT)-specific T-cell clones obtained from atopic and nonatopic subjects were compared. The proportion of TT-specific clones with the Th2 profile of cytokine production was significantly higher in atopics than in nonatopics. More importantly, even if almost all PPD-specific clones from both atopics and nonatopics were able to produce IFN- γ , a clear difference emerged with regard to their ability to produce IL-4. Indeed, about 40% of PPD-specific T-cell clones derived from atopics, but only 5% of those derived from nonatopics, produced IL-4 in response to stimulation by the specific antigen (31). These data suggest that atopic patients have enhanced ability to produce IL-4, even in response to antigens other than allergens or helminthic components.

The molecular alteration or alterations responsible for the enhanced ability of helper T cells from atopics to produce IL-4 and IL-5 are unknown. They may represent, however, one of the hallmarks of atopic status, which is currently being investigated.

Conclusions

In the last few years great progress in the knowledge of the cellular and molecular signals responsible for IgE antibody synthesis and induction of allergic inflammation has been made. There is a general consensus that IL-4 and IFN- γ are the main regulatory cytokines of IgE production, with opposite effects. Their physiological role has clearly been established

by both *in vitro* and *in vivo* studies. Moreover, convincing evidence is accumulating that Th cells producing IL-4 and IL-5, but not producing, or producing only limited amounts of, IFN- γ , and that resemble murine Th2 cells, accumulate in the blood and/or target organs of patients with helminth infections or atopic disorders. These cells can account for both the IgE antibody formation and the eosinophilia seen in these patients.

The mechanisms responsible for the preferential expansion of Th2 cells in atopics and in patients with helminth infections are currently under investigation. We have shown that virtually all T-cell clones specific for components of the helminth *Toxocara canis*, and derived from the peripheral blood of normal individuals, display the Th2 phenotype of cytokine secretion, whereas almost all PPD-specific T-cell clones obtained from the same donors belong to the Th1 cell subset. This finding strongly suggests that these two antigens may influence in opposite ways the profile of cytokine secretion of Th cells. It remains to be established whether the preferential ability of helminth components to expand Th2 cells is related to their molecular structure, to the type of antigen-presenting cells (APC) involved in their processing, and/or to other microenvironmental influences at the site of immunization.

The reason why environmental allergens induce IgE antibody responses, but only in a minority of individuals (so-called atopics), represents a still more complex question. At least two genetic traits seem to be involved in the control of IgE antibody responses in atopic subjects. First, the responsiveness to individual allergens is controlled by Ir genes linked to the MHC. This means that Th cells able to recognize allergen epitopes can be substantially activated only in subjects possessing appropriate individual sequences in the MHC class II products of APC. This might explain why allergen-specific T-cell clones can be easily derived from allergen-sensitive patients, but not from randomly selected nonatopic individuals. Once recognized, allergens induce the preferential differentiation of Th cells into lymphocytes with the Th2 phenotype of cytokine secretion. As for helminthic components, this may be due to particular features of allergen structure, to the type of APC involved in their processing, or to other, still unknown, microenvironmental influences. The role of additional genes not linked to MHC that control the total serum IgE levels reflecting overall IgE responsiveness has also been suggested. However, the nature of these genes, as well as the mechanisms by which they exert their control, is still unknown. Our results indicate that atopic patients have higher proportions of IL-4-producing T cells than do nonatopics even at the level of PPD- or TT-specific T-cell repertoires. Although it does so indirectly, this find-

ing suggests that a deregulation in the production of IL-4 may be responsible for the increase of overall IgE responsiveness in atopic individuals.

The cytokines produced by activated, allergen-specific Th2 lymphocytes are involved not only in the ongoing production of IgE, but also in the triggering and maintenance of allergic inflammation in tissues. As mentioned before, Th2 cells can produce IL-3 and IL-4 (which favor the growth, differentiation, and activation of mast cells), IL-5 (which promotes eosinophil growth and differentiation), and IL-6 and GM-CSF (which facilitate the formation of inflammatory tissue infiltrates).

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