

Restricted Lymphokine Synthesis in CD4+ Helper T Cells: New Insights into the Regulation of IgE Synthesis and the Pathogenesis of Allergic Disease

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ABSTRACT

Over the past 5 years, a greater appreciation has developed regarding the role that IgE plays in the pathogenesis of allergic disease and asthma. Clinical investigators have shown that elevated IgE levels strongly correlate with the presence of asthma. In addition, other investigators have demonstrated that crosslinking of IgE on the surface of mast cells not only results in the release of histamine and other mediators but also produces a cascade of events leading to late phase reactions, bronchial hyperreactivity, and an allergic inflammatory response. Recent studies of the effects of a number of factors produced by CD4+ helper T lymphocytes—in particular, interleukin (IL) 4, IL-5 and IL-3—indicate that a distinct subtype of CD4+ T lymphocytes producing a specific profile of lymphokines greatly increases the secretion of IgE from B cells and enhances the accumulation of eosinophils and mast cells in the allergic inflammatory response. Thus, a complex network of cell types, including B cells producing IgE, mast cells, eosinophils, and subsets of CD4+ T lymphocytes secreting specific profiles of lymphokines, is involved in the development and regulation of allergic inflammation. This new understanding of allergic inflammatory disease and its dependence on IgE and on lymphokine synthesis in subsets of CD4+ T cells will lead to improved strategies in the treatment and control of allergic diseases.

INTRODUCTION

IT HAS BEEN KNOWN for several decades that IgE molecules that are bound to high-affinity Fc receptors for IgE (FcεR1) on mast cells mediate type 1 allergic immediate hypersensitivity responses. Exposure to allergen results in crosslinking of these allergen-specific IgE molecules on mast cells and leads to a cascade of events that include the degranulation of the mast cell and release of a host of inflammatory mediators that initiate the allergic reaction.

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The importance of IgE in allergic disease has become even more apparent with recent observations regarding the pathogenesis of asthma. New investigations in three broad areas concerning asthma all indicate that IgE and mast cells play a critical role not only in the initiation but also in the maintenance of the allergic state. These three areas of current investigation are (1) the definition of IgE-mediated inflammatory reactions,^(1,2) (2) the examination of the role of bronchial hyperreactivity in the pathogenesis of asthma,^(3,4) and (3) the finding that the occurrence of asthma is highly correlated with elevated serum IgE levels.⁽⁵⁾ Thus, the role of IgE is even more consequential than once thought in the pathogenesis of allergic disease.

In the first part of this review, we discuss these new concepts regarding the role of IgE as a key effector molecule in allergic disease. In the second part, we review the immunologic events that are involved in the regulation of IgE synthesis and summarize our new understanding of the role of CD4+ helper T cells in this process. A great deal has been learned recently about the biology of CD4+ T cells and the regulation of lymphokine synthesis in these cells. We focus on this area as it relates to CD4+ T cells in allergic and nonallergic individuals and as it relates to the regulation of IgE synthesis. CD4+ T lymphocytes have been found to be heterogeneous and can be separated into subsets that produce nonoverlapping profiles of lymphokines.⁽⁶⁻⁸⁾ This concept—that specific lymphokines are coordinately expressed in CD4+ T cells—is particularly important in the regulation of IgE synthesis and allergic reactions and is likely to provide insight into why only some individuals and not others develop IgE and allergic responses when exposed to allergen. This may lead to innovative strategies for therapeutic intervention in the treatment and control of allergic diseases.

ANALYSIS OF IgE-DEPENDENT ALLERGIC INFLAMMATORY RESPONSES

The first area of clinical investigation of allergic disease that we discuss is the important concept that allergic responses are complex and prolonged, involving a large number of mediators produced by multiple cell types.^(1,2) Although histamine released from mast cells plays a prominent role in the immediate phase of allergic reactions, other mediators and lymphokines released from mast cells and other cell types (eosinophils, lymphocytes, and macrophages) that are attracted to sites of allergic reactions play equally important roles in the genesis of the allergic inflammatory response. Thus, the traditional concept that allergic reactions are mediated solely by IgE and mast cells has been greatly expanded.

Although the histopathology of early type 1 immediate hypersensitivity responses reveals only tissue edema with minimal cellular infiltrate, biopsies of bronchial mucosa of chronic asthmatics have confirmed that fully developed allergic inflammatory responses are characterized not only by the presence of mast cells secreting histamine and leukotrienes but also by the infiltration of a large number of eosinophils, lymphocytes, and macrophages and by the shedding of normal ciliated epithelium.^(9,10) Eosinophils in these lesions are activated and produce a host of mediators, including platelet-activating factor (a very potent chemotactic factor for eosinophils) and eosinophil major basic protein (a factor that is highly toxic for tissue). T lymphocytes also are quite conspicuous in mucosal biopsy specimens and, as we discuss later, secrete a variety of factors that amplify and perpetuate the allergic inflammatory response. The release of vasoactive substances, proteinases, and toxic mediators by these cells results in mucosal injury, as manifested by epithelial desquamation. The prominence of eosinophils and of epithelial shedding has suggested the description “chronic desquamating eosinophilic bronchitis” for asthma, which emphasizes the importance of the histopathology that develops in the allergic inflammatory response.

The inflammation and consequent tissue damage associated with allergic reactions can be reproduced experimentally by inhalation of allergen in sensitive individuals. Such a procedure provokes an immediate or early-phase response due to crosslinking of IgE molecules on mast cells and subsequent histamine release, which often is followed in 6–8 hours by a late-phase response that is usually more severe and more difficult to reverse than the early phase response.⁽¹¹⁾ Late-phase responses are associated with both the development of persistent airway inflammation, characterized by the infiltration of eosinophils, lymphocytes, and macrophages, and the desquamation of respiratory epithelium. As a consequence of the late-phase response, bronchial and/or nasal hyperreactivity develops. In this way, mast cell degranulation is translated into the allergic inflammatory response and into the clinical manifestations of allergic disease.

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ANALYSIS OF BRONCHIAL HYPERREACTIVITY

The second area of investigation that has highlighted the role of IgE in allergic disease is the description and analysis of bronchial hyperreactivity.^(3,4,12) Bronchial hyperresponsiveness, which is an exaggerated bronchoconstrictor response to stimuli, correlates closely with the severity of asthma and is now thought to be a primary characteristic of the disease.⁽¹³⁾ Nasal hyperresponsiveness is a similar condition, correlating with the severity of allergic rhinitis. There is considerable experimental evidence that bronchial and nasal hyperreactivity is related directly to the degree of inflammation present in the airways.^(12,13) Furthermore, patients who respond to allergen exposure with late-phase reactions develop an increase in airway responsiveness that can persist for weeks after allergen exposure.⁽¹⁴⁾ In contrast, allergen avoidance reduces bronchial hyperreactivity. These studies indicate that bronchial hyperreactivity is clinically important and results directly from the allergic inflammatory response initiated by crosslinking of IgE on the surface of mast cells.

DIRECT ASSOCIATION OF ELEVATED IgE AND ASTHMA

The third new concept regarding IgE and allergic disease is that elevated serum IgE is associated strongly with the development of asthma. IgE-mediated mechanisms have been recognized for many years as the basis of allergic rhinitis, and, as just described, studies performed with bronchial allergen challenge in allergen-sensitive patients indicate that IgE and mast cells initiate an inflammatory reaction, which results in the development of bronchial hyperresponsiveness. A large number of asthmatics, however, have been presumed traditionally to be nonallergic and to have intrinsic asthma, mediated by mechanisms unrelated to IgE-mediated allergic inflammatory reactions. It turns out, however, that virtually all patients with asthma may have disease that involves IgE-related mechanisms. In a large population-based study, Burrows et al. demonstrated that elevated total serum IgE is an important risk factor for asthma, irrespective of whether or not atopy can be demonstrated by skin tests.⁽⁵⁾ The prevalence of asthma was shown to increase directly with increasing IgE, and no asthma was seen in individuals with the lowest total IgE levels. Thus, serum IgE levels were the best predictors of asthma, emphasizing the importance of IgE and mast cells in the pathogenesis of asthma.

Although not all investigators may agree with the suggestion of Burrows et al. that allergy plays a major role in every patient with asthma,⁽⁵⁾ the results of many other studies indicate that an inflammatory response characterized by the presence of mast cells, eosinophils, T cells, and macrophages is indeed present and persistent both in patients with severe asthma and in those with milder disease.⁽¹⁰⁾ In the next section of this review, we discuss the advances that have occurred in our understanding of the regulation of IgE synthesis and the biology of CD4+ helper T cells. These findings, delineating the network of biologic factors that interrelate IgE synthesis, mast cells, eosinophils, and CD4+ T cells, have provided insights into the cellular and molecular basis for IgE-mediated allergic inflammatory reactions and have given us clues as to how such responses are regulated and perpetuated in allergic individuals.

REGULATION OF IgE SYNTHESIS

The CD4+ helper T cell is the key cell that orchestrates the synthesis of IgE.^(8,15,16) Activation of B cells normally is dependent on exposure of the B cell to specific antigen as well as to signals delivered to the B cell by CD4+ T cells, and this is true for the activation of B cells destined to produce IgE. The CD4+ T cell provides signals that not only activate but also instruct the B cell to differentiate and produce a particular immunoglobulin isotype (for example, IgG or IgE). The specifics of these processes only recently have been elucidated, primarily due to (1) the availability of recombinant lymphokines and cytokines and (2) techniques to study helper CD4+ T cells at the clonal level.

Lymphokines and cytokines: The mediators of immune function

Cytokines are protein molecules produced by many cell types (lymphocytes produce cytokines, which also are known as lymphokines) that exert their biologic effects by interaction with specific cytokine receptor molecules located on the surface of target cells. Molecular biologic techniques have allowed the production of recombinant cytokine proteins, the availability of which has allowed the precise characterization of these products. CD4⁺ T cells and the cytokines that they produce have a very broad spectrum of bioactivity that includes mediating and modulating immune responses and promoting and regulating cell growth. In addition, cytokines are involved in inflammatory responses to infection, in the pathophysiology of shock and fever, and in the production of acute phase reactants. Each cytokine has multiple activities and conversely, each activity can be mediated by several different cytokines (Table 1). Thus, the immune system is redundant and complex. Before the cloning of cytokine genes and the availability of recombinant cytokine proteins, investigators could not separate the activities of mixtures of cytokines produced by bulk populations of T cells, primarily because

TABLE 1. INTERLEUKINS AND THEIR FUNCTIONS

<i>Interleukin</i>	<i>Source</i>	<i>Function</i>
IL-1	Macrophages	Costimulatory effect on T cells Enhance antigen presentation
IL-2	T cells	T cell growth factor B cell growth factor
IL-3	T cells Mast cells	Mast cell growth factor Multicolony (including mast cell) stimulating factor
IL-4 (BSF-1)	T cells Mast cells	T cell growth factor Enhances IgE synthesis Enhances murine IgG1 synthesis Mast cell growth factor Increases Ia expression on B cells Increases CD23 expression on B cells and macrophages
IL-5 (TRF)	T cells	Enhances immunoglobulin synthesis Enhances IgA synthesis Enhances eosinophil differentiation
IL-6 (BSF-2)	T cells Macrophages Fibroblasts Endothelial	Enhances immunoglobulin synthesis Antiviral activity Hepatocyte-stimulating factor
IL-7	Stromal cells	Enhances growth of pre-B cells Mitogenic for thymocytes
IL-8	Mononuclear cells	T cell chemotactic factor Neutrophil-activating protein
IL-10	Th2 and B cells	Inhibits IL-2 and IFN- γ synthesis Enhances Ia expression on B cells
IFN- γ	T cells	Enhances murine IgG2a synthesis Inhibits murine IgE synthesis Antiviral activity
LMW-BCGF	T cells	Enhances B cell proliferation Enhances IgE synthesis
GM-CSF	Multiple types	Promotes growth/differentiation of granulocytes and macrophages
TNF- α	T and NK cells Macrophages Mast cells	Tumoricidal activity, produces cachexia, fever, prostaglandin synthesis Activates macrophages and neutrophils

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many cytokines have mutually antagonistic qualities. The cloning of the genes for these cytokines has allowed precise characterization of the activity in purified cytokine proteins and has resulted in the development of definitive assays for each cytokine.

Using recombinant cytokine proteins and specific cytokine assays, it has become apparent that certain combinations of cytokines specifically occur together during certain types of immune responses. For example, in humoral immune responses, T cells produce interleukins 4, 5, and 6 (IL-4, IL-5, IL-6), which are cytokines important in B cell activation and differentiation.⁽¹⁶⁾ In contrast, during delayed type-hypersensitivity responses, interferon- γ (IFN- γ) and tumor necrosis factor α (TNF α) are invariably present, presumably because both are important in the activation of macrophages.⁽¹⁷⁾ IL-4, which inhibits the activation of macrophages, is not present during such responses. Thus distinct and nonoverlapping profiles of cytokines are observed during specific types of immune responses.

SPECIFICITY IN THE TYPE OF IMMUNE RESPONSE

There are two categories of specificity in immunology: the first category is the traditional one that involves discrimination between self and nonself and depends on recognition of foreign substances using antigen-specific receptors on B cells and T cells. The second category of specificity is related to the type of immune response that is generated on antigen challenge, and this second kind of specificity is dependent on the regulation of the production of specific cytokine profiles by CD4+ T cells. The profile of cytokines produced during an immune response appears to be essential in determining immune specificity in terms of the type of immune response that is generated.

It has been known for several decades that when antigen is injected into an animal, both humoral immunity (immunoglobulin synthesis) and cell-mediated immunity (delayed-type hypersensitivity responses) can be induced. It is now recognized that both types of responses are mediated by CD4+ helper T cells but that different pathogenic organisms show remarkable variation in their capacity to preferentially induce these types of responses. For example, pathogens that proliferate intracellularly in macrophages (e.g., mycobacteria, *Toxoplasma*, *Leishmania*, or *Listeria*) induce only delayed-type hypersensitivity immune responses and not immunoglobulin synthesis.^(17,18) In contrast, other pathogens, such as extracellular bacteria, induce immunoglobulin synthesis, and helminths and allergens preferentially induce IgE synthesis.^(19,20) Although delayed-type hypersensitivity responses can occur simultaneously with antibody production in response to a particular antigen, in many instances in both clinical and experimental infections, the development of one type of response is incompatible with the other, so that in such cases, immunoglobulin synthesis and delayed-type hypersensitivity are mutually exclusive. Since CD4+ helper cells are involved in both humoral immunity and delayed-type hypersensitivity responses, the means by which these cells regulate the generation of specific types of immune responses has been uncertain for many years.

Heterogeneity among CD4+ helper T cells

One possible mechanism by which CD4+ helper T cells regulate the type of immune response is that CD4+ T cells are heterogeneous, such that the CD4+ T cell involved in delayed-type hypersensitivity is distinct from and produces a cytokine profile different than that involved in the induction of IgG or IgE synthesis. The availability of techniques to study helper CD4+ T cells at the clonal level, i.e., by examining CD4+ T cells cultured from single cells, has allowed investigators to determine that CD4+ T cells are indeed heterogeneous and that they segregate into two basic types: CD4+ T helper cells, designated as Th1, synthesize IL-2 and IFN γ , and other CD4+ T helper cells, designated as Th2, do not synthesize IL-2 or IFN γ but instead produce IL-4, IL-5, and IL-6^(6-8,15) (Table 2). Th1 cells are important in mediating delayed-type hypersensitivity,⁽²¹⁾ whereas Th2 cells are important in the induction of immunoglobulin synthesis, particularly of the IgE isotype.^(15,16) Th1 and Th2 cells appear, therefore, to correspond to the two poles in the spectrum of types of immune response. On recognition of different classes of antigens or pathogens, the appropriate type of helper T cell may be selectively activated and expanded, resulting in the selective production of cytokines and the generation of a specific type of immune response.

TABLE 2. TWO TYPES OF MURINE CLONED T CELL LINES

<i>Function</i>	<i>Th1</i>	<i>Th2</i>
Surface markers		
CD4	+	+
CD8	—	—
Synthesis of		
IL-2	+	—
IFN- γ	+	—
Lymphotoxin	+	—
IL-4	—	+
IL-5	—	+
IL-10 (CSIF)	—	+
Delayed-type hypersensitivity	+	—
Receptors for IL-1	—	+
B cell help	$\pm$	+
IgE synthesis	—	+
IgG2a synthesis	+	—

T CELL SIGNALS REQUIRED FOR THE INDUCTION OF IgE SYNTHESIS

Using Th2 clones and recombinant cytokines, a number of investigators have determined that the cytokine IL-4 is absolutely required for IgE synthesis.^(6–8,15,16) Induction of IgE synthesis occurred only when B cells were cultured with Th2 clones that produced IL-4 or when recombinant IL-4 was added to the cultures. In addition, monoclonal antibody against IL-4 inhibited IgE synthesis in helminth-infected mice.⁽²⁰⁾ IL-4 was shown to cause isotype switch, meaning that it instructs the B cell to undergo rearrangement of the immunoglobulin heavy chain gene locus, resulting in a switch from production of IgM to production of IgE.⁽¹⁶⁾

Although IL-4 is required for IgE synthesis, it is not sufficient, since purified B cells cultured only with IL-4 do not synthesize antibody. Other factors are necessary, including low-molecular-weight B cell growth factor,⁽¹⁵⁾ IL-6,⁽²²⁾ and an as yet uncharacterized signal from T cells, generated by the direct physical interaction of B cell and T cell (cognate interaction signal).⁽¹⁵⁾ This latter signal may be transduced from the B cell surface via the cell surface antigen CD40, since human B cells treated with anti-CD40 monoclonal antibody and cultured with IL-4 can produce IgE.⁽²³⁾ It is clear that Th2 cells, which produce IL-4 but not IFN γ , are very adept in providing the necessary signals to B cells for the induction of IgE synthesis.^(16,24) In contrast, Th1 clones cannot induce B cells to synthesize IgE and may, in fact, produce some factors (such as IFN γ) that are actually inhibitory for IgE synthesis. Thus, the selective activation of Th2 cells may be the fundamental immunologic event that culminates in induction of the IgE inflammatory response and may be the fundamental event that propagates and sustains allergic inflammatory responses.

THE IgE-MEDIATED INFLAMMATORY CELL NETWORK

The importance of the specific combination of cytokines produced by Th2 clones in IgE-mediated inflammatory responses is emphasized further by the fact that the Th2 profile of cytokines (IL-3, IL-4, IL-5, and IL-6) not only affects IgE synthesis but also modulates and regulates mast cell and eosinophil growth and differentiation. IL-3, also known as mast cell growth factor, plus IL-4 specifically upregulate mast cell growth, and IL-3 plus IL-5 specifically enhance eosinophil growth.⁽²⁵⁾ Thus, monoclonal antibody against IL-5 injected into mice will inhibit eosinophilia but will have minimal or no effect on serum IgE levels.⁽²⁶⁾ Since IL-4 is thus almost always produced in combination with IL-5, it is now easy to understand why elevated serum IgE levels, eosinophilia, and mast cell expansion occur together.

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Whereas Th2 cells appear to produce most of the particular combination of cytokines that modulate IgE synthesis, mast cell, and eosinophil growth, a similar combination of cytokines also is synthesized by mast cells.⁽²⁷⁾ Thus, mast cells have been shown to produce IL-4 and also may secrete IL-3, IL-5, and IL-6. This indicates that mast cells not only are effector cells releasing mediators in the allergic inflammatory response but also participate in the regulation and modulation of the inflammatory response. Therefore, an integrated network of cells produces this particular combination of cytokines that are involved in the genesis and amplification of the allergic inflammatory response (Fig. 1).

The model proposing that Th2 cells (with mast cells), which produce a specific cytokine profile, orchestrate not only IgE synthesis but also IgE-mediated inflammatory responses is supported by several lines of experimental evidence. First, in biopsies of allergy skin test sites in humans who have developed both immediate and late phase skin test reactions (the dermal equivalent of early-and-late phase responses in the lung), the presence of the Th2 profile of cytokines (IL-4 and IL-5, but not IFN γ) was demonstrated.⁽²⁸⁾ In addition, CD4+ T cell clones isolated from allergic individuals and specific for *Dermatophyoides pteronyssinus* (dust mite allergen) produced IL-4 but not IFN γ , whereas CD4+ clones from the same individual but specific for nonallergens, such as tetanus toxoid or *Candida albicans*, produced IFN γ but little or no IL-4.⁽²⁹⁾

These results indicate that the division of CD4+ T cells into Th1 and Th2 subsets is of fundamental relevance to the regulation of isotype-specific responses and to the regulation of responses to different classes of antigens. In allergic individuals, allergen exposure results in the development of Th2 cells that produce large quantities of IL-4 and IL-5, which in turn activate B cells to produce IgE and stimulate mast cell and eosinophil proliferation. In nonallergic individuals, it is thought that exposure to the same allergen results in an entirely different type of immune response, in which the T cells that are activated produce IFN γ and other factors that inhibit IgE synthesis and mast cell/eosinophil proliferation.

It should be noted that the combination of cytokines produced by Th1 clones (the Th1 profile, which includes IFN γ and other cytokines) is extremely important in other clinical settings. For example, in leprosy

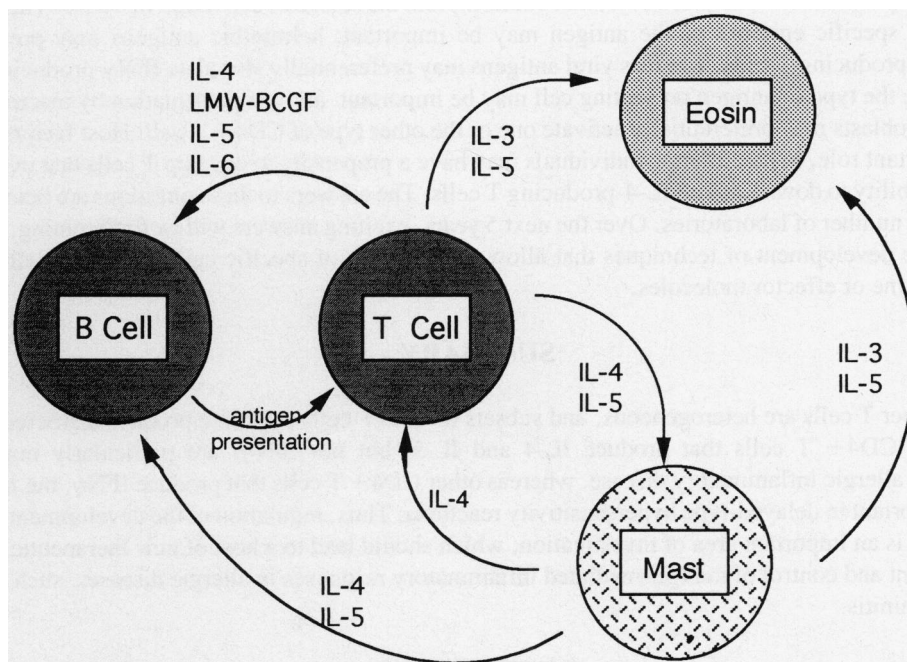


FIG. 1. Cell types and factors involved in positive regulation in IgE synthesis and in the allergic inflammatory response. The T cell represents a Th2 cell, producing multiple factors that have effects on B cells in the induction of IgE synthesis, on eosinophils (Eosin) and mast cells. Negative regulation, e.g., by IFN γ , produced by Th1 cells is not represented here.

or leishmania infection, delayed-type hypersensitivity and IFN γ synthesis are required for abrogation of the infection, and development of the Th2 profile of cytokines (IL-4 plus IL-5) in this instance instead of the Th1 profile (IFN γ) is associated with disseminated infection.^(17-19,30) Thus, activation of CD4+ T cell subsets with inappropriate cytokine profiles appears to result in the development of allergic disease or susceptibility to specific types of infection.

SPECTRUM OF CD4+ T CELL TYPES

Although there is a large body of experimental evidence to support the Th1/Th2 dichotomy model for regulation of immune responses, the model may be oversimplified, representing only the ends of a spectrum of CD4+ T cell types. In addition, because the Th1 and Th2 dichotomy was described initially in the murine system, there is still considerable controversy about the existence of such a dichotomy in humans. However, studies have confirmed that Th1 and Th2 clones do exist in human as well as in mice, although additional patterns of cytokine profiles have been identified^(7,15,30,31) both in mice and in humans, and single T cells with unrestricted profiles producing both IFN γ and IL-4 have been isolated. The important concept, though, is that restricted cytokine patterns do exist in humans, forming a basis for mechanisms that allow for the development of specific types of immune responses.

Although this new understanding of the complexity of CD4+ T cells may explain the regulation of the type of immune response that develops on encounter with a particular antigen, it poses further interesting questions. For example, are Th1 and Th2 clones derived from separate lineages, or do they differentiate from a common precursor? What are the parameters that regulate the development of CD4+ T cells with restricted cytokine profiles? How can one selectively activate IL-4-producing (or conversely IFN γ -producing) T cells? Recent reports investigating mechanisms that might selectively activate Th1 or Th2 T cells have demonstrated the mutually antagonistic effects of cytokines produced by Th1 and Th2 clones. IFN γ , produced by Th1 clones, has been shown to inhibit the proliferation of Th2 clones.⁽³²⁾ On the other hand, IL-10, produced by Th2 clones, has been found to inhibit the production of IFN γ by Th1 cells.⁽³³⁾ Thus, predominant activation of one subset has been shown to suppress the activation or function of the other.

Many other possibilities exist, however, that could explain the selective activation of Th1 vs Th2 cells. For example, the specific epitopes of the antigen may be important: helminthic antigens may preferentially activate IL-4-producing T cells, whereas viral antigens may preferentially stimulate IFN γ -producing T cells. Alternatively, the type of antigen presenting cell may be important: antigen presentation by macrophages vs B cells or fibroblasts may preferentially activate one or the other type of CD4+ T cell. Host factors also may play an important role, in that allergic individuals may have a propensity to develop T cells that overproduce IL-4 or an inability to downregulate IL-4-producing T cells. The answers to these questions are being pursued zealously in a number of laboratories. Over the next 5 years, exciting answers will be forthcoming, mainly as a result of the development of techniques that allow the isolation of specific cell types or activities and of specific cytokine or effector molecules.

SUMMARY

CD4+ helper T cells are heterogeneous, and subsets of CD4+ cells exist that produce restricted cytokine profiles. The CD4+ T cells that produce IL-4 and IL-5, but not IFN γ , are particularly important in IgE-mediated allergic inflammatory disease, whereas other CD4+ T cells that produce IFN γ , but not IL-4 or IL-5, are important in delayed-type hypersensitivity reactions. Thus, regulation of the development of CD4+ T cell subsets is an important area of investigation, which should lead to a host of new therapeutic strategies in the treatment and control of the IgE-mediated inflammatory responses in allergic diseases, such as asthma and allergic rhinitis.

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