New millennium: The conquest of allergy

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The role of lymphocytes in allergic disease

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In the last few years strong evidence has accumulated to suggest that allergen-reactive type-2 T helper (T_H2) cells play an important role in the induction and maintenance of the allergic inflammatory cascade. First, cytokines and chemokines produced by T_H2 cells (GM-CSF, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, macrophage-derived chemokine) and those produced by other cell types in response to T_H2 cytokines or as a reaction to T_H2-related tissue damage (eotaxin, transforming growth factor-β, IL-11) account for most pathophysiologic aspects of allergic disorders (production of IgE antibodies; recruitment or activation of mast cells, basophils, and eosinophils; mucus hypersecretion; subepithelial fibrosis; and tissue remodeling). The T_H2 hypothesis may also explain the complex genetic background responsible for allergic disorders. Several genes are involved in the development and regulation of T_H2 cells and may provide the reason why the prevalence of atopic allergy is increasing in Western countries. Indeed, a dramatic change has occurred in the last several decades in the "microbial" environment of children, thus probably altering the balance between T_H1 and T_H2 responses to "innocuous" antigens (allergens) in favor of T_H2 responses. Finally, the T_H2 hypothesis offers exciting opportunities for the development of novel immunotherapeutic strategies targeted to address allergen-specific T_H2 cells or T_H2-derived effector molecules in atopic individuals. (J Allergy Clin Immunol 2000;105:399-408.)

Key words: *T_H1/T_H2 cells, atopy, cytokines, chemokines, hygiene hypothesis, oligodeoxynucleotides, allergy, asthma, allergic rhinitis*

Abbreviations used

APC:	Antigen-presenting cell
DC:	Dendritic cell
Dp:	*Dermatophagoides pteronyssinus*
LAG-3:	Lymphocyte activation gene-3
LIF:	Leukemia inhibitory factor
MDC:	Macrophage-derived chemokine
NF-AT:	Nuclear factor of activated T cells
NIP45:	NF-AT–interacting protein
NK:	Natural killer
ODN:	Oligodeoxynucleotide
STAT:	Signal transducer and activator of transcription
TCR:	T-cell receptor
TGF-β:	Transforming growth factor-β
T_H1:	Type 1 T helper
T_H2:	Type 2 T helper

There have been two main phases in the history of discoveries on the pathogenesis of atopic allergy. The first phase started in 1879, when Ehrlich[1] first described mast cells and eosinophils, includes the discovery of reagins by Prausnitz and Kustner[2] in 1921, and ended in 1967 with the identification of the IgE nature of reaginic antibodies, independently performed by Ishizaka and Ishizaka[3] and Johansson.[4] The concept of allergic reaction emerging at the end of this phase was that of an inflammatory process sustained by the interaction between common environmental allergens and specific IgE antibodies bound to IgE receptors on mediator-releasing mast cells.

The second phase started in 1986 with the discovery of T-cell–derived cytokines that regulate the IgE antibody production by B cells, performed by Coffman and Carty[5] in mice and by Del Prete et al[6] and Pene et al[7] in humans, includes the description of type 1 (T_H1) and type 2 (T_H2) T helper cells by Mosmann et al[8] in mice and by Del Prete et al[9] in humans, and is still going on. Currently, because of many other discoveries that have not been mentioned here, the allergic reaction appears to be the result of a T_H2-type T-cell response to one or more common environmental allergens. The allergen-specific T_H2 response represents the triggering event for the recruitment and the involvement of the other cell types, as well as a large number of soluble factors and adhesion molecules, thus resulting in an inflammatory cascade of unequaled complexity. On the basis of these findings, atopic allergy may be defined as a T_H2-driven hypersensitivity to innocuous antigens (allergens) of complex genetic and environmental origins. In recent years the "T_H2 hypothesis in allergy" has been accepted by the majority of authors[10] (Table I).

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TABLE I. Conceptual and experimental data supporting the "T_H2 hypothesis" in atopic allergy

Conceptual
T_H2 cells are only cells that can both directly recognize allergen peptides (TCR) and account for joint involvement of IgE-producing B cells (IL-4, IL-13), mast cells (IL-4, IL-10), and eosinophils (IL-5) in allergic inflammation
Experimental
In humans
Allergens evoke T_H2 responses in atopic subjects[11,12]
T_H2 cells accumulate in target organs of atopic subjects[13-15]
Successful specific immunotherapy shifts allergen-specific response from T_H2 to T_H1[16-19]
In murine models
Transfer of T_H2 cells into recipient mice induces airway eosinophilia, mucus hypersecretion, and AHR[20,21]
Allergy and asthma are not inducible in gene-deficient animal models resulting in a deficiency of T_H2 responses[22-25]
Transgenic mice that overexpress T_H2 cytokines in airway epithelium exhibit airway eosinophilia, mucus hyperproduction, AHR, and airway remodeling[26-30]

TCR, T-cell receptor; AHR, airway hyperresponsiveness. Modified from Romagnani S. The Th2 hypothesis in allergy—"Eppur si muove!" Allergy Clin Immunol Intern 1998;10:158-65.

DEFINITION AND PROPERTIES OF T_H2 CELLS

T_H2 cells represent a polarized form of the T helper cell–mediated immune response characterized by the production of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 but not of IFN-γ and TNF-β. By contrast, the other polarized form of the T helper cell response, which is defined as T_H1, is characterized by the production of IL-2, IFN-γ, and TNF-β but not of the T_H2-type cytokines.[8,9] The T_H1/T_H2 polarization is clear-cut in the murine models on the basis of artificial immunization or infection, whereas it is usually less restricted among human T helper cells.[31] In general, T_H1-polarized responses are highly protective against infections mounted by the majority of microbes, especially the intracellular parasites, because of the ability of T_H1-type cytokines to activate phagocytes and to promote the production by B lymphocytes of opsonizing and complement-fixing antibodies (phagocyte-dependent host defense). However, when the microbe is not rapidly removed from the body, the T_H1 response may become dangerous for the host because of the strong and chronic inflammatory reaction evoked. By contrast, the cytokines produced by T_H2 cells induce the differentiation, the activation, and the in situ survival of eosinophils (through IL-5), promote the production by B lymphocytes of high amounts of antibodies, including IgE (through IL-4 or IL-13), as well as the growth of mast cells and basophils (through IL-4, IL-9, and IL-10). Moreover, IL-4, IL-10, and IL-13 inhibit several macrophage functions or the development of T_H1 cells. Thus the phagocyte-independent T_H2 response is usually less protective than the T_H1 response against the majority of infectious agents, with the exception of some gastrointestinal nematodes.[32] However, T_H2 cells probably play an important regulatory role in the immune system because a switch from T_H1 to T_H2 may provide a protective effect when the T_H1 response threatens to become a dangerous event for the host.[31,33]

Besides the selective production of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, human T_H2 cells also exhibit the preferential release of leukemia inhibitory factor (LIF), which is very important for egg implantation and therefore for successful pregnancy,[34] and of macrophage-derived chemokine (MDC),[35] which probably contributes to an amplification circuit in allergic inflammation.[36] Moreover, human T_H2 cells exhibit the preferential expression of some surface molecules, such as CD30, CCR4, CCR8, and CRTH2,[10] whereas human T_H1 cells preferentially express lymphocyte activation gene-3 (LAG-3), CXCR3, and CCR5,[10] the chemokine receptors being probably important for the recruitment and homing in target tissues of T_H2 or T_H1 cells, respectively.

FACTORS RESPONSIBLE FOR T_H2 POLARIZATION

In the last few years the factors responsible for the polarization of the specific immune response into a predominant T_H1 or T_H2 pathway have been extensively investigated. Current evidence suggests that T_H1 and T_H2 cells are not derived from distinct lineages but rather develop from the same T helper cell precursor under the influence of both environmental and genetic factors acting at the level of antigen presentation. Among the environmental factors, a role for the route of antigen entry, the physical form of immunogen, the type of adjuvant, and the dose of antigen has been suggested.[10,31,33] The genetic mechanisms that concur in controlling the type of T helper cell differentiation still remain elusive. The environmental and genetic factors mixed together can influence the T_H1/T_H2 differentiation mainly by modulating (1) a group of contact-dependent factors and (2) the predominance of a given cytokine in the microenvironment of the responding Th cell. Among contact-dependent factors the most important are (1) the extent of TCR ligation[37] and (2) the signals delivered by OX4OL-OX40 and B7-CD28 interactions.[38,39] OX40 costimulation enhances IL-4 expression at priming and promotes the differentiation of naive CD4 T cells into high IL-4–producing effectors.[38] The role of B7-CD28 interactions is more complex and still contro-

versial. However, IL-4 production by naive T cells also appears to be highly dependent on B7 molecules.[39] Naive $CD4^+$ T cells seem to be receptive to CD28-dependent IL-4 production only if they receive a weak TCR signal.[40] Thus naive T helper cells themselves are able to produce small amounts of IL-4 from their initial activation, and the concentration of IL-4 that accumulates at the level of the T helper cell response increases with increasing lymphocyte activation. The inducing effect of IL-4 dominates over other cytokines, so that if IL-4 levels reach a necessary threshold differentiation of the T helper cell into the T_H2 phenotype occurs. Under certain circumstances another IL-4 source may be a small subset of $CD4^+NK1.1^+$ cells capable of recognizing antigens presented in association with the nonpolymorphic β_2-microglobulin–associated molecule CD1.[41] Finally, the role of IL-4 released by mast cells or basophils in promoting the differentiation of T helper cells into the T_H2 pathway has been suggested. However, IL-4 released by mast cells/basophils may amplify established T_H2 responses, but its role in promoting the development of T_H2 cells in the primary response is unlikely because obvious mechanisms determining FcεR-independent IL-4 production for the majority of antigens have not been defined yet. In contrast to IL-4, the early production of IL-12, IL-18, and IFNs (α and γ) favors the development of T_H1 cells.[42-45] IL-12, which is the most powerful T_H1-inducing agent, is mainly produced by dendritic cells (DC) under the stimulation provided by exogenous signals and is up-regulated by both CD40L/CD40 interaction and the presence of IFN-γ. Of interest, IFN-γ, but not IFN-α, promotes the T_H1 differentiation in mice, whereas both IFN-γ and IFN-α play an important role in humans,[42,43] IFN-α up-regulating the expression of the IL-12 receptor β chain.[46]

TRANSCRIPTION FACTORS THAT REGULATE THE DEVELOPMENT OF T_H2 CELLS

The demonstration that early IL-4 expression during an immune response is critical for determining the development of T_H2 cells has raised interest in the molecular basis of its regulation. The binding of cytokines to their receptors typically results in rapid tyrosine phosphorylation of signal transducers and activators of transcription (STATs). Of these, STAT6 appears selectively activated by IL-4 and knockout of *Stat6* gene results in deficient T_H2 responses, inasmuch as in these animals T cells are unable to develop into T_H2 cells and the production of IgE and IgG_1 is virtually abolished.[47] However, there is yet no direct evidence that STAT6 transactivates the IL-4 promoter in T cells or that the STAT6 site of the IL-4 promoter is required for promoter activity. Other transcription factors of the nuclear factor of activated T cells (NF-AT) family (NF-ATp, NF-ATc, NF-AT3, NF-AT4) are able to transactivate the IL-4 promoter, but they are expressed in both T_H1 and T_H2 cells.[48] However, in NF-ATc–deficient chimeric mice severe T-cell defects in IL-4 production and T_H2 differentiation were observed.[49] By contrast, NF-ATp–deficient mice displayed increased T_H2 and decreased T_H1 responses, suggesting that, unlike NF-ATc, NF-ATp behaves as negative regulator of the T_H2 responses.[49] Another molecule that appears to be a repressor of the T_H2 responses is the proto-oncogene Bcl-6, which inhibits STAT6 transcription.[50] Bcl-6 has been shown to repress IL-4–induced activation of CD23 expression and targeted deletion of the Bcl gene led to a massive inflammatory response characterized by eosinophilic infiltration. Moreover, IgE responses were elevated in immunized Bcl-6–deficient mice.[50,51] NF-AT interacting protein (NIP45) is also a factor expressed in T_H2 cells that appears to function as a potent coactivator of IL-4 gene transcription,[52] but its expression in T_H1 cells is unclear. Other transcription factors expressed by many cell types are important for T_H2 gene expression. Mice genetically deficient in the nuclear factor-κB subunit p50 failed to express IL-5 and eotaxin, as well as to develop airway inflammation.[53] The transcription factors C/EBP and activator protein-1 have also been shown to be important for the expression of T_H2 cytokine genes.[49,54] Finally, the proto-oncogene c-*maf* is selectively expressed in T_H2 clones and is induced during T_H2, but not during T_H1, differentiation.[55] More important, its activity appears to be specific for the IL-4 promoter, inasmuch as it is unable to transactivate the promoters of other T_H2 cytokine genes, such as IL-5 or IL-10. A transcription factor that may be more widely involved in the induction and maintenance of the T_H2 pattern of cytokine secretion is GATA-3. GATA-3 is expressed in both immature and mature T cells and is selectively suppressed during T_H1, but not during T_H2, differentiation.[56] Thus, in contrast to c-*maf*, which appears to be IL-4–specific, GATA-3 may function as a more general regulator of T_H2 cytokine expression.[57] However, the hierarchy of transcription factors and their differential control in T_H2 gene expression, as well as the precise relationship between the different factors, are still unclear.

MECHANISMS RESPONSIBLE FOR ALLERGEN-SPECIFIC T_H2 RESPONSES IN ATOPIC INDIVIDUALS

It is well known that the expression of the allergic phenotype is dependent on 2 major factors: a genetic predisposition and the environmental interactions.

Genetic predisposition

It is clear that the pattern of allergic inheritance does not follow the mendelian concepts usually associated with single-gene diseases. Rather, the pattern of inheritance is that of a complex polygenic disorder. This is consistent with the fact that the development of a prevalent T_H2 response is up- and down-regulated by the activity of a series of cytokines, cytokine receptors, and transcription factors. Therefore alterations may be localized in atopic individuals at multiple genes and may differ in different subjects. This makes it impossible, despite the

present availability of new powerful technologies, to identify major common genetic alterations responsible for atopic allergy.[58]

Environmental factors acting before birth

Environmental factors may influence the differentiation of allergen-specific T cells into a prevalent T_H2 phenotype and therefore the development of atopic allergy by acting both before and after birth. Some years ago we first showed that the immune response to *Dermatophagoides pteronyssinus* (Dp) begins during fetal life,[59] a finding that has since been confirmed by others.[60,61] In pregnancy a T_H2-skewed priming probably occurs in all cases because of the maternal environment. Successful pregnancy may indeed be characterized by a switch from T_H1 to T_H2 at the maternal-fetal interface to reduce the reactivity of the maternal immune system against the fetal allograft.[62] Accordingly, progesterone, at the concentrations present at the fetal-maternal interface, favors the development of T cells into IL-4–producing cells.[63] More recently, we found that T-cell clones generated from the decidua of women with unexplained recurrent abortions showed significantly reduced production of IL-4, IL-10, and LIF in comparison with T-cell clones generated from the decidua of women with underlying voluntary abortion (normal gestation).[34] Thus the pregnancy-related environment may favor a weak T_H2-skewed priming to transplacental allergens, which is obviously enhanced under the influence of an "atopic" genetic background.[61]

Environmental factors acting after birth

Enviromental factors acting after birth, however, are certainly more important in influencing the individual outcome in the T helper cell response to ubiquitous allergens and can account for the increased prevalence of allergy over the last decades in Western countries. Indeed, a genetic mechanism with steep changes in gene frequency is highly unlikely in the absence of extraordinary mutation rates or very powerful darwinian selection. More important, we know that after the occurrence of random TCR rearrangements and the processes of positive and negative selection in the thymus the educational process of the immune system continues in the periphery, especially in the first years of life, throughout repeated interactions with infectious agents, "innocuous antigens," and the commensal flora. This process results in both a fine tuning of the TCR repertoire and the progressive shifting of the T-cell effector balance from T_H2 to T_H1. Based on this knowledge and on our data showing that cytokines (IL-12 and IFNs) produced by cells of the "natural immunity," such as macrophages, DCs, and natural killer (NK) cells, in response to *Mycobacterium tuberculosis* or its components were able to shift, at least in vitro, the development of allergen-specific T cells from the T_H2/T_H0 to the T_H1 profile,[42-44] 6 years ago I hypothesized that the increasing prevalence of allergy could be related to changes that occurred in the infectious environment of children after the second world war rather than to pollution.[64] This hypothesis has been confirmed by studies performed in mice showing that IFN-γ produced during the T_H1 immune response against BCG suppresses the development of local inflammatory T_H2 responses in the lung.[65] More important, several epidemiologic studies strongly suggest that changes in the infectious environment and in the pattern of microbial exposure of children associated with Westernization are an important factor underlying the rising severity and prevalence of atopic disorders over the last decades in developed countries (Table II). The major causes of changes in the microbial environment that alter the balance between T_H1 and T_H2 responses in favor of T_H2 and support the validity of the so-called "hygiene" hypothesis are summarized in Fig 1.

MULTIPLE ROLE OF T_H2 CELLS IN THE INITIATION AND MAINTENANCE OF ALLERGIC INFLAMMATION

The role of T_H2 cells in allergic inflammation is not limited to their ability to induce the production of allergen-specific IgE antibodies by B cells and to promote the eosinophilic infiltration in target tissues. Recent data suggest that at least some pathophysiologic consequences of allergic reactions may occur in the absence of the IgE response. Indeed, B-cell–,[72] IgE-,[73] CD40-,[74] and mast cell-[75] gene deficient mice can develop asthma, whereas $CD4^+$ T-cell-21, IL-4-22, STAT6-23, and IL-5-24 gene deficient mice cannot. Of note, in IL-4–gene deficient mice, only the passive transfer of T, but not of non-T, cells may restore both their ability to develop T_H2 cells and to produce IgE antibodies.[22] Thus IL-4 produced by T cells seems to be essential for the development of T_H2 cells and therefore for the production of both IgE antibodies and IL-5; however, IL-5–mediated effects appear to be even more important than IL-4–related activities at the effector level. Accordingly, it has been suggested that T_H2 cells may play a pathogenic role even in intrinsic asthma,[76] which means that a "true" T_H2 phenotype characterizes asthma independent of the etiology. Moreover, we have recently shown that penicillin-specific T cells have a strongly T_H2-polarized profile even in penicillin-allergic patients with late clinical manifestations and apparently showing no penicillin-specific IgE antibodies in their serum.[77] It is of note that IL-4, IL-5, and IL-13 produced by T_H2 cells can account directly or indirectly for the great majority of the pathophysiologic manifestations of allergic patients. IL-4 is not only responsible for the IgE isotype switching, thus explaining the involvement of FcεR1-positive (mast cells/basophils) in the response to allergen, but also for the rolling on and adhesion to, endothelial cells of circulating eosinophils,[78] which can then be attracted into the target tissue by both IL-5 and eotaxins.[79] It is of note that the eotaxin receptor (CCR3) is expressed not only by eosinophils[80] but also by basophils[81] and mast cells,[82,83] whereas the presence of CCR3 on T_H2 cells,[84] if any, does not seem to be a relevant phenomenon in vivo.[83,85] Moreover, eotaxin is pro-

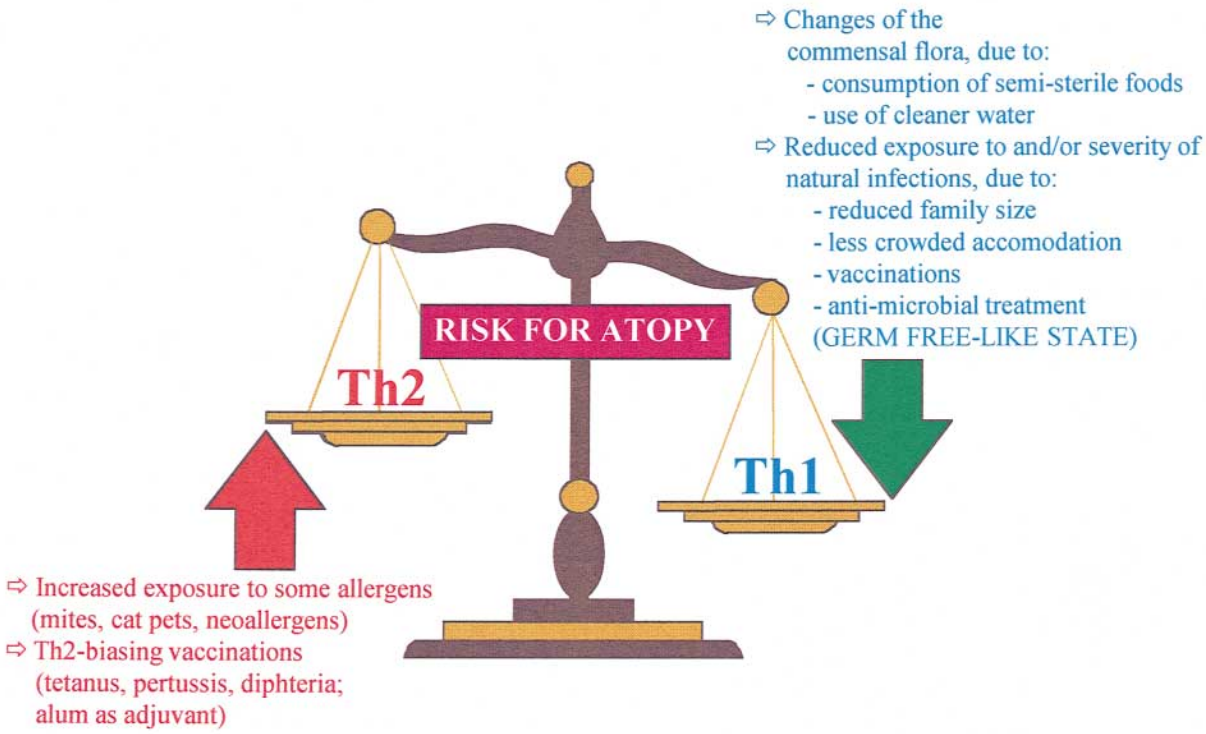

FIG 1. Factors that have contributed to change infectious environment during childhood, thus favoring the alteration of balance between T_H1 and T_H2 responses to innocuous antigens (allergens) in favor of T_H2 responses.

TABLE II. Main epidemiologic studies supporting "hygiene" hypothesis

Increased number of siblings decreases risk for allergy, which is higher in firstborn[66]
There is inverse relationship between risk for atopy and occurrence of some infections in childhood[67,68]
There is reduced prevalence of allergy/asthma in patients with multiple sclerosis, a T_H1-mediated disorder[69]
Total serum IgE levels decline in subjects infected by parasites after treatment for tuberculosis[70]
Prevalence of atopy is lower in children from anthroposophic families[71]

duced by epithelial cells, endothelial cells, and fibroblasts under the positive control of IL-4 or IL-13.[86-88] In turn, eotaxin potentiates antigen-dependent basophil IL-4 production.[89] Finally, IL-4, IL-9, and IL-13 are responsible for mucus hypersecretion by, and induce metaplasia of, mucus cells.[30,89] IL-4 and IL-13 stimulate fibroblast growth and chemotaxis, as well the synthesis of extracellular matrix proteins,[90-92] and IL-5 and IL-9 favor subepithelial fibrosis.[28,29,93] Subepithelial fibrosis also results from the activity of transforming growth factor-β (TGF-β) produced by eosinophils and fibroblasts[94,95] and of IL-6 produced by several cell types including T_H2 cells themselves.[30,96] Of note, IL-11 expressed by eosinophils and epithelial cells causes an airway phenotype characterized by subepithelial fibrosis, enhanced deposition of collagen, and enhanced accumulation of fibroblasts, myofibroblasts, and myocytes.[30,97] The fact that this cytokine also inhibits the acute eosinophilic response and T_H2 gene expression suggests that it may represent a healing molecule in the airway.[30] Taken all together, these findings suggest that T_H2 cytokines, either directly or indirectly, can also contribute to airway remodeling in asthma. Finally, MDC produced by T_H2 cells in addition to DCs interacts with the CCR4 receptor present on the same cells, and both IL-4 and IL-13 stimulate the production of MDC by DCs, thus providing another important amplification circuit for allergic inflammation.[35,36] Accordingly, overproduction of T_H2-specific chemokines MDC and thymus and activation-regulated chemokine (TARC), as well as hyperexpression of their receptor CCR4, have recently been described in NC-Nga mice exhibiting atopic dermatitis–like lesions.[98] The multiple direct and indirect effects of T_H2 cytokines in the genesis of the inflammatory allergic cascade and in the tissue damage of allergic disorders and bronchial asthma are summarized in Fig 2.

POSSIBLE T_H2-BASED NOVEL IMMUNOTHERAPEUTIC STRATEGIES IN ALLERGIC DISORDERS

The "T_H2 hypothesis" and the new insights in the pathogenesis of allergic disorders provide exciting opportunities for the development of novel immunomod-

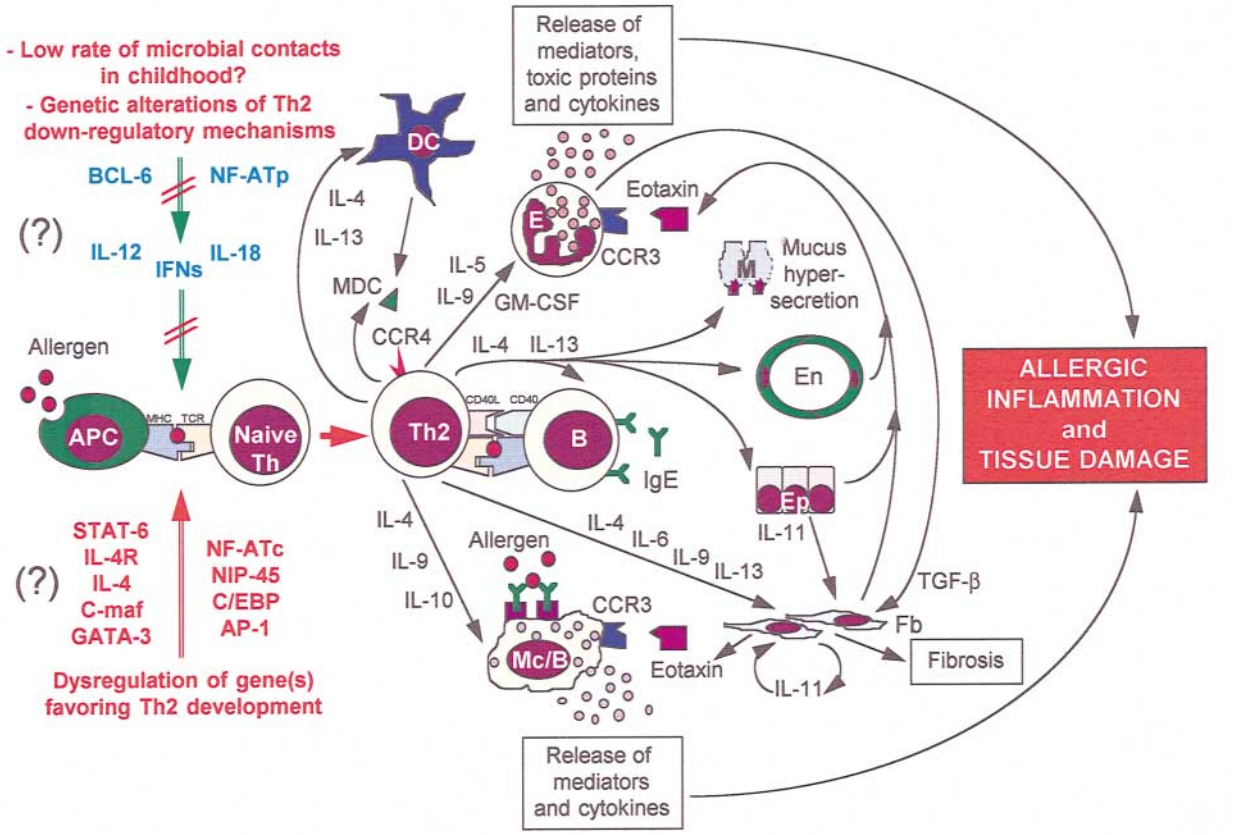

FIG 2. Multiple role of T_H2 cells in allergic inflammatory cascade and in pathogenesis of tissue damage in bronchial asthma (for explanations, see text). *APC,* Antigen-presenting cell; *B,* B lymphocyte; *E,* eosinophil; *Mc/B,* mast cell/basophil; *Ep,* epithelial cell; *M,* mucus cell; *En,* endothelial cell; *Fb,* fibroblast.

TABLE III. Possible novel immunotherapeutic strategies for allergic disorders on the basis of the "T_H2 hypothesis"

Targeting allergen-specific T_H2 cells
Induction of anergy in T_H2 cells by allergen-derived peptides
Redirection of allergen-specific T_H2 responses
Allergen plus T_H1-inducing cytokines
Altered allergen peptide cytokines
Allergen peptides incorporated in recombinant microorganisms or appropriate adjuvants
Plasmid DNA (allergen epitope) gene therapy
Allergen conjugated with appropriate ODNs
Targeting development of T_H2 cells or production of T_H2-related effector molecules
Selective blockers of T_H2 transcription factors (c-Maf, STAT6)
IL-4 inhibitors (soluble IL-4 factors, IL-4 mutant protein)
IL-5 inhibitors (anti-IL-5 antibody, inhibitors of IL-5 transcription)
IL-13 inhibitors (soluble IL-13 receptors)
IgE inhibitors ("intelligent" anti-IgE antibody)

Modified from Parronchi P, Maggi E, Romagnani S. Redirecting Th2 responses in allergy. Curr Topics Microbiol Immunol 1999;238:27-56.

ulatory regimens. These approaches may be addressed to target allergen-specific T cells (allergen-specific immunotherapy) or their effector molecules (nonallergen-specific immunotherapy)[99] (Table III). In patients with severe atopic disorders, the possibility of nonallergen-specific immunotherapeutic regimens designed to target T_H2 cells or T_H2-dependent effector molecules such as the specific IL-4 transcription factors IL-4, IL-5, IL-13, and IgE are being considered.[100-104] Allergen-specific immunotherapy, which is probably more appropriate in the majority of atopic subjects, may include the induction of nonresponsiveness in allergen-specific T_H2 cells by allergen peptides or redirection of allergen-specific T_H2 responses by T_H1-inducing cytokines, altered peptide ligands, allergens incorporated into recombinant microorganisms or bound to appropriate adjuvants, plas-

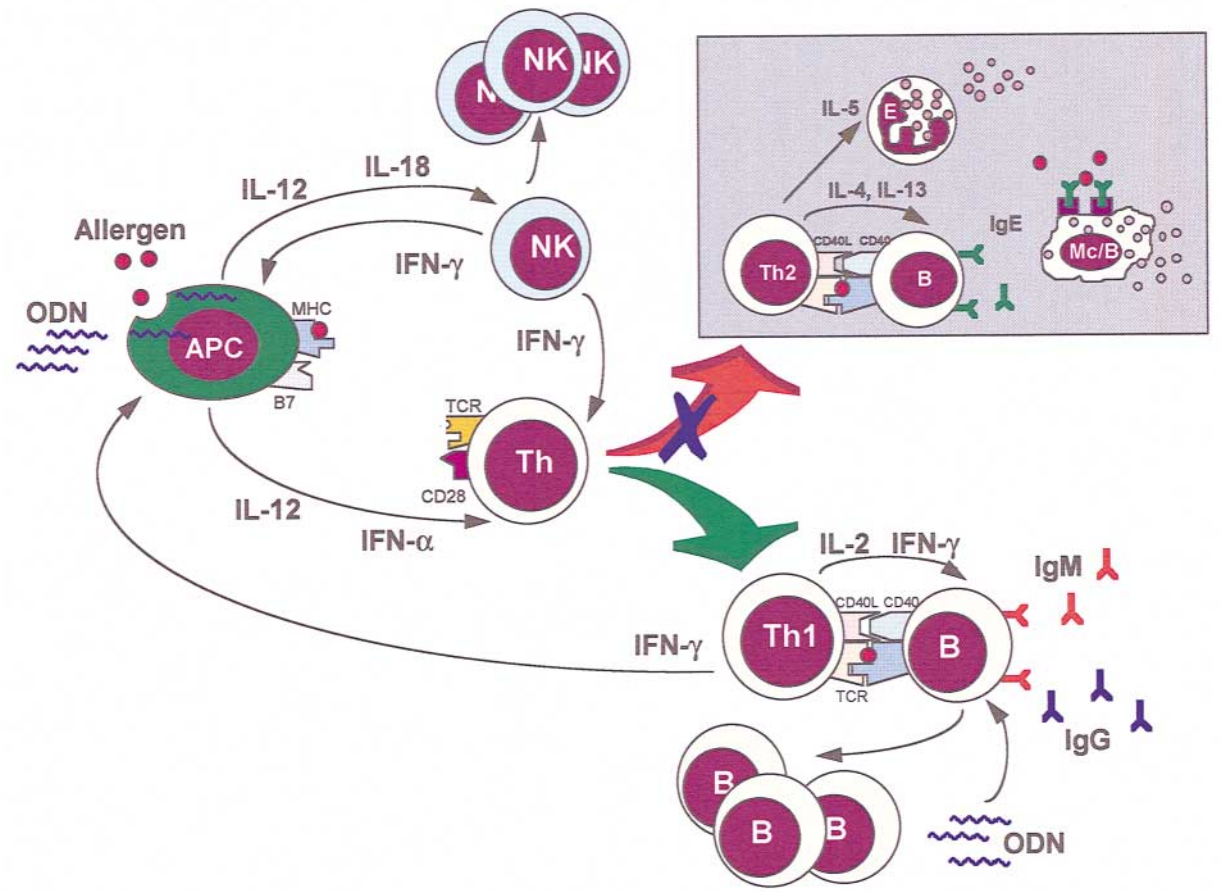

FIG 3. Effects of ODNs containing appropriate motifs on immune response and their possible use for shifting allergen-specific T-cell response from T_H2 to T_H1.

mid DNA vaccination, or allergens conjugated to appropriate oligodeoxynucleotides (ODNs).[105-115] This latter approach appears to be particularly promising, as shown by studies performed in both murine models in vivo and human T cells in vitro. CpG-motif–containing ODNs are able to inhibit IL-5 production, eosinophilic inflammation, and airway hyperresponsiveness in mice[110,111] by shifting the specific immune response to a T_H1-dominated profile of cytokine production.[114] Some ODNs were also found to be able to shift the differentiation of Dp group 1–specific human $CD4^+$ T cells from atopic donors into T helper cell effectors showing a prevalent T_H1, instead of T_H2, cytokine profile.[115] This effect was mediated by the ability of these ODNs to induce the production of T_H1-inducing cytokines by monocytes, DCs, and NK cells (Fig 3), although it was apparently related to motifs at least partially different[115] from those previously defined to be active in mice.[112,113] Thus injecion of allergen(s) mixed to, or modified by conjugation with, appropriate motifs containing ODNs may provide a new immunotherapeutic strategy for the treatment of human allergic disorders.

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