

The Th1/Th2 paradigm and allergic disorders

Romagnani S. The Th1/Th2 paradigm and allergic disorders.
Allergy 1998; 53 (Suppl 46): 12-15. © Munksgaard 1998.

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In recent years, the great progress achieved in the knowledge of helper T (Th) cell functions has provided the explanation for the joint involvement of IgE-producing B cells, mast cells/basophils, and eosinophils in the pathogenesis of allergic inflammation. This novel view, which has been defined as the "Th2 hypothesis in allergy", suggests that atopy is a Th2-driven hypersensitivity to innocuous antigens (allergens) of complex genetic and environmental origins (1, 2). The data supporting the Th2 hypothesis in allergy are both conceptual and experimental. First, Th2 cells are the only cells that can directly recognize allergen peptides and account for both mast-cell and eosinophil involvement in the allergic cascade. Secondly, allergens evoke Th2 responses in atopics, and Th2 cells accumulate in the target organs of atopics. Finally, successful specific immunotherapy shifts the allergen-specific response from the Th2 to the Th1 pattern (1, 2).

Evolution of the definition of Th2 cells

According to their profile of cytokine production, Th2 cells represent one of the two polarized forms of the CD4⁺ Th cell-mediated effector response. In the mouse, Th1 cells secrete interleukin (IL)-2, tumor necrosis factor (TNF)- β , and interferon (IFN)- γ and are the principal effectors of the phagocyte-mediated host defense, which is highly protective against infections by intracellular parasites (3). On the other hand, murine Th2 cells produce IL-4 and IL-13, which stimulate IgE and IgG1 antibody production; IL-5 (an eosinophil-activating factor); and IL-10, which, together with IL-4 and IL-13, inhibits several macrophage functions, thus providing better protection against

infections by complex parasites, such as some intestinal helminths. Although human T-cell clones with characteristics similar to murine Th1 and Th2 clones exist as well (4, 5), such a strict dichotomy including all cytokines as described in mice is rarely found in man. Therefore, a more realistic definition may be that Th1 cells are CD4⁺ effector T cells able to produce IFN- γ , but not IL-4, whereas Th2 are CD4⁺ effector T cells which produce IL-4, but not IFN- γ (6, 7). Whatever definition is used, the Th1/Th2 model provides an interesting paradigm for the study and the understanding of several pathophysiologic processes and possibly for the development of novel immunotherapeutic strategies.

Why do allergens induce Th2 responses in atopic subjects?

It is now reasonable to hypothesize that the preferential development of Th2 cells in response to allergens in atopic subjects is determined by:

- 1) the nature and the intensity of TCR signaling by the allergen peptide ligand
- 2) the altered regulation of IL-4 production by Th cells and/or other cell types, which is probably controlled by both genetic and environmental factors.

Genetic factors

The possibility that atopic subjects have a genetic dysregulation at the level of Th cell-derived IL-4 is supported by several observations. First, CD4⁺ T-cell clones from atopic individuals are able to

produce noticeable amounts of IL-4 and IL-5 in response to bacterial antigens, such as PPD and streptokinase, that usually evoke responses with a restricted Th1-like cytokine profile in nonatopic individuals (8). Second, there is a linkage of overall IgE to markers in chromosome 5q31.1, especially to the IL-4 gene (9). Third, atopic subjects have a higher frequency of IL-4-producing T cells than normal subjects (10). Fourth, T-cell clones generated from cord-blood lymphocytes of neonates with atopic parents produce higher IL-4 concentrations than neonatal lymphocytes of neonates with nonatopic parents (11). Finally, polymorphism in the proximal IL-4 promoter has been identified (12). Recently, large panels of *Parietaria officinalis* group 1 (Par 1)-specific T-cell clones were generated from donors with low or high serum IgE levels and assessed for both profile of cytokine production and reactivity to two immunodominant Par 1 peptides (p92 and p96). Of note, both p92- and p96-specific T-cell clones generated from "high IgE" donors produced remarkably large amounts of IL-4 and little IFN- γ . In contrast, the majority of p96-specific T-cell clones generated from "low IgE" donors produced large amounts of both IL-4 and IFN- γ , whereas most p92-specific T-cell clones generated from the same donors showed a Th1-like profile (high IFN- γ and low IL-4) (13). Taken together, these data strongly suggest that the allergen peptide ligand can influence the cytokine profile of Th cells, but the mechanisms underlying noncognate regulation of IgE responsiveness are overwhelming.

The alterations favoring the preferential Th2 response with subsequent abnormal IgE production in atopics may be at the level of intracellular signalings involved in Th2-cell development. It is now clear that, after the interaction between IL-4 and its receptor on a given cell, the IL-4-induced-signal transducer and activator of transcription (STAT) protein, initially designated IL-4 STAT and hereafter termed STAT6, is activated. STAT6 is related in primary amino-acid sequence to STAT1, yet is encoded by a different gene. The essential role of STAT6 in IL-4 signalling has clearly been demonstrated in STAT6-deficient mice. In these animals, T cells are indeed unable to develop into Th2 cells, and production of IgE and IgG1 is virtually abolished (14, 15). However, there is still 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. On the other hand, other transcription factors of the nuclear factor of activated T cells (NF-AT) family can transactivate the IL-4 promoter, but they are expressed in both Th1 and Th2 cells (16). Thus, it is unlikely that these factors can explain the Th2-

specific expression of the IL-4 gene. NIP45 (NF-AT interacting protein) is another factor expressed in Th2 cells which appears to function as a potent coactivator of IL-4 gene transcription (17). However, its expression in Th1 cells is unclear. In contrast, the proto-oncogene *c-maf* appears to be selectively expressed in Th2 clones and is induced during Th2, but not during Th1, differentiation (18). Moreover, its activity appears to be specific to the IL-4 promoter, inasmuch as it is unable to transactivate the promoters of other Th2 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 Th2 pattern of cytokine secretion is GATA-3 (19). GATA-3 is expressed in both immature and mature T cells, and is selectively suppressed during Th1, but not during Th2, differentiation (20). Thus, in contrast to *c-maf*, which appears to be IL-4-specific, GATA-3 may function as a more general regulator of Th2 cytokine expression (21).

Another site of dysregulation in the development of allergen-specific Th2 responses in atopics may be at the level of genes coding for IL-4 receptor subunits. Recently, in high proportions of patients with atopic disorders, a mutation in the gene structure of the IL-4 receptor (IL-4R) α subunit has been described, which seems to account for the increased avidity in the IL-4 binding to its receptor and higher expression of CD23 antigen by B cells (22). Whether this alteration also results in enhanced response of naive T cells to IL-4, thus favoring the preferential Th2 response to allergen(s), remains to be determined.

Environmental factors

The observation that the prevalence of allergy has been increasing over the last decades in developed countries suggests that, in addition to genetic alterations at the level of mechanisms governing IL-4 and/or IL-4R gene expression, environmental factors acting either before or after birth also contribute to regulate the development of Th2 cells and/or their function. Some years ago, we first showed that the immune response to *Dermatophagoides pteronyssinus* begins during fetal life (23), a finding which has since been confirmed by others (24, 25). During pregnancy, Th2-skewed priming probably occurs in all cases, due to the maternal environment. Successful pregnancy may indeed be characterized by a switch from Th1 to Th2 in order to reduce the reactivity of the maternal immune system to the fetal allograft (26). Accordingly, progesterone, at the concentrations present at the fetomaternal interface, aids the development of T cells into IL-4-producing cells (27). More recently,

we found that T-cell clones generated from the decidua of women suffering from unexplained recurrent abortions showed significantly reduced production of IL-4, IL-10, and leukemia inhibitory factor in comparison with T-cell clones generated from the decidua of women with underlying voluntary abortion (normal gestation) (28). Thus, the pregnancy-related environment may favor a weak Th2-skewed priming to transplacental allergens, which is obviously enhanced under the influence of an "atopic" genetic background (29).

The environmental factors acting after birth, however, are certainly more important in influencing the individual outcome in the Th response to ubiquitous allergens, and they probably account for the increased prevalence of allergy over the last decades in Westernized countries. Four years ago, when the increased prevalence of allergy was generally attributed to pollution, we proposed that it could rather be "at least partly related to the strong reduction in childhood (just when aeroallergen sensitization is occurring) infections, particularly tubercular infection, which previously induced the production of cytokines antagonistic to Th2 development" (1). This hypothesis was mainly based on our data showing that cytokines (IL-12 and IFNs) produced by cells of the "natural immunity" (macrophages, natural killer cells) in response to *Mycobacterium tuberculosis* and/or its components were able to shift, at least *in vitro*, the development of allergen-specific T cells from the Th2/Th0 to the Th1 profile (7, 29). This possibility is in keeping with the results of recent experiments showing that IFN- γ produced during the Th1 immune response in BCG-infected mice suppresses the development of local inflammatory Th2 responses in the lung (30). More importantly, at least three epidemiologic studies strongly support the concept that the decline of repeated and severe infections in childhood is an important factor underlying the rising severity and prevalence of atopic disorders over the last decades in developed countries (31–33). Major causes of changes in infectious diseases and in the pattern of microbial exposure which are associated with Westernization include cleaner water and food; less crowded accommodation; and changes in the natural history of exposure due to better nutrition, vaccinations, and antimicrobial treatments.

Concluding remarks

The Th2 hypothesis and the new insights into the pathogenesis of allergic disorders provide exciting opportunities for the development of novel immunomodulatory regimens. These novel approaches may target allergen-specific T cells (allergen-

specific immunotherapy) or their effector molecules (nonallergen-specific immunotherapy) (reviewed in Ref. 2). Allergen-specific immunotherapy includes induction of nonresponsiveness in allergen-specific Th2 cells by allergen peptides or redirection of allergen-specific Th2 responses by Th1-inducing cytokines, altered peptide ligands, allergens incorporated into recombinant microorganisms or bound to appropriate adjuvants, and plasmid DNA vaccination. In patients with severe atopic disorders, the possibility of nonallergen-specific immunotherapeutic regimens designed to target Th2 cells or Th2-dependent effector molecules, such as specific IL-4 transcription factors, IL-4, IL-5, and IgE, are also being considered.

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