Allergic asthma is a complex disorder characterized by local and systemic allergic inflammation and reversible airway obstruction. Asthma symptoms, especially shortness of breath, are primarily related to airway obstruction, and death is almost invariably due to asphyxiation (7). Increased airway responsiveness to provocative stimuli, termed airway hyperresponsiveness (AHR), and mucus hypersecretion by goblet cells are two of the principal causes of airway obstruction observed in asthma patients (2). Data from animal models consistently reveal a critical role for T_{h2} cells (T helper 2 cells) and potentially important roles for the cytokines IL-4 and IL-5 (3–7).

T_{h2} cells selectively develop and expand in the presence of IL-4 (8). To separate direct effects of IL-4 from developmental effects on T_{h2} cells in an asthma model, we compared the ability to establish the asthma phenotype in BALB/c mice deficient in either IL-4 or the IL-4 receptor α chain (IL-4Rα) (9). After intranasal challenge with the antigen ovalbumin (OVA), BALB/c mice developed a stereotyped asthma phenotype characterized by eosinophil influx of the airways, goblet cell metaplasia with mucus overproduction, and an increase in AHR as revealed by enhanced sensitivity to acetylcholine challenge (6, 7). IL-4 and IL-4Rα-deficient mice showed incremental attenuation of each of these asthma indices (Fig. 1, C through E) (10). Thus, in agreement with prior studies (5–7), IL-4 contributes to the asthma phenotype, but these data suggest an independently greater contribution by IL-4Rα.

IL-13 is a cytokine closely related to IL-4 that binds to IL-4Rα and is also expressed by T_{h2} cells from asthma patients (11). To assess whether IL-13 might contribute to the asthma phenotype in BALB/c mice deficient in either IL-4 or the IL-4 receptor α chain (IL-4Rα) (9). After intranasal challenge with the antigen ovalbumin (OVA), BALB/c mice developed a stereotyped asthma phenotype characterized by eosinophil influx of the airways, goblet cell metaplasia with mucus overproduction, and an increase in AHR as revealed by enhanced sensitivity to acetylcholine challenge (6, 7). IL-4 and IL-4Rα-deficient mice showed incremental attenuation of each of these asthma indices (Fig. 1, C through E) (10). Thus, in agreement with prior studies (5–7), IL-4 contributes to the asthma phenotype, but these data suggest an independently greater contribution by IL-4Rα.

Fig. 1. PAS-stained histologic sections of murine lungs. Arrowheads point to goblet cells within the respiratory epithelium. (A) Wild-type mice were primed with OVA and challenged with PBS intranasally. (B) Wild-type mice were administered IL-13 intranasally. (C) IL-4–deficient and (D) IL-4Rα–deficient mice were primed with OVA and challenged with OVA intranasally. Wild-type mice were primed with OVA and challenged intranasally with (E) OVA and human Fc control protein or with (F) OVA and IL-13Rα-Fc. Note the marked reduction in goblet cells in (D) and (F).
phenotype, we administered a soluble IL-13 receptor α2-human Fc fusion protein (IL-13R-Fc) to BALB/c mice sensitized to OVA and compared them to mice that received control protein (12). IL-13R-Fc selectively binds to and neutralizes murine IL-13 but not IL-4 (13). This treatment significantly attenuated the asthma phenotype, although little effect was seen on neutrophil influx into bronchoalveolar lavage (BAL) (Figs. 1, E and F, and 2). Thus, IL-13, like IL-4 (5–7), can contribute to the acute effector phase of experimental asthma.

To assess the capacity of IL-13 and IL-4 to cause pathology independently of T and B cells, we administered each cytokine to nonimmunized BALB/c and RAG1-deficient mice (14). Each cytokine alone induced the asthma phenotype (Figs. 1, A and B, and 3). In contrast, administration of either cytokine to IL-4Rα-deficient mice resulted in no significant changes in any asthma parameter, demonstrating that their effects were dependent on signals mediated by IL-4Rα. Further, adoptive transfer of OVA-specific Tγδ2 cells to IL-4Rα-deficient mice failed to elicit the asthma phenotype, whereas identical treatment of wild-type mice resulted in the full phenotype (15, 16). Thus, experimental asthma induced by antigen challenge, recombinant cytokine, or adoptive transfer of Tγδ2 cells, is mediated through a final pathway dependent on IL-4Rα.

Attenuated asthma phenotypes observed in IL-4–deficient mice may now be interpreted as representing the effects of residual IL-13 derived from IL-4–deficient Tγδ2 cells (17). Parallel observations in experimental intestinal helminth infections demonstrate roles for both IL-4 and IL-13 in mediating critical final effector pathways via IL-4Rα (18). It is possible that human asthma represents a spectrum of diseases also linked by a shared receptor effector pathway. The common embryological origin of tissues from the gut and lung (19) would support the presence of stereotyped responses in these organs.

The relevance of our data to human asthma remains an important issue that cannot be entirely addressed, given the complexity of the disease and the inadequacies of any animal model. Linkage analysis has mapped susceptibility to asthma to a region on human chromosome 5q25-31, which includes the genes for both IL-4 and IL-13 (20), and to mutations in two domains of the α chain of the IL-4 receptor (21). A number of additional regions in the genome have been linked to asthma in human studies, suggesting a complex multifactorial phenotype (22). As we suggest, however, diverse forms of asthma might follow a final common effector pathway mediated through signals transduced by IL-4Rα, thus creating a unified target for potential intervention.

References and Notes
14. Wild-type, BALB/c IL-4—/— (23) and C57BL6/RAG1—/— (24) mice were purchased from Jackson Laboratory. BALB/c IL-4Rα−− were obtained at the Max-Planck-Institut für Immunobiologie. Mice were immunized and intranasally challenged with chicken egg OVA (6, 7). AHR was expressed as the provocative concentration of acetylcholine (in milligrams per kilogram) that increased baseline airway resistance 200% (PC200).
15. Data for (A) AHR, (B) goblet cell score, and numbers of (C) eosinophils and (D) neutrophils in the BAL fluid are plotted as means ± SEM. *P < 0.05 relative to mice receiving control protein. Data are representative of at least two comparable experiments with four to eight mice per group.

Fig. 2. Effect of neutralization of IL-13. Primed wild-type mice were administered intranasally human immunoglobulin (Ig control), Ig control and OVA, or IL-13R-Fc and OVA as indicated by (+). Data for (A) AHR, (B) goblet cell score, and numbers of (C) eosinophils and (D) neutrophils in the BAL fluid are plotted as means ± SEM. *(P < 0.05 relative to PBS and Ig control–treated mice; †p < 0.05 relative to OVA and Ig control–treated mice. Data are representative of at least two comparable experiments with four to eight mice per group.

Fig. 3. Effect of recombinant IL-4 and IL-13. Wild-type (WT), RAG1-deficient (RAG1−−), and IL-4Rα-deficient (IL-4Rα−−) mice were administered IL-4, IL-13, or control protein intranasally. Data for (A) AHR, (B) goblet cell score, and numbers of (C) eosinophils and (D) neutrophils in the BAL fluid are plotted as means ± SEM. *(P < 0.05 relative to mice receiving control protein. Data are representative of at least two comparable experiments with four to eight mice per group.
Molecular Basis of T Cell Inactivation by CTLA-4

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CTLA-4, a negative regulator of T cell function, was found to associate with the T cell receptor (TCR) complex ζ chain in primary T cells. The association of TCRζ with CTLA-4, reconstituted in 293 transfectants, was enhanced by p56lck-induced tyrosine phosphorylation. Coexpression of the CTLA-4–associated tyrosine phosphatase, SHP-2, resulted in dephosphorylation of TCRζ bound to CTLA-4 and abolished the p56lck-inducible TCRζ–CTLA-4 interaction. Thus, CTLA-4 inhibits TCR signal transduction by binding to TCRζ and inhibiting tyrosine phosphorylation after T cell activation. These findings have broad implications for the negative regulation of T cell function and T cell tolerance.

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CD4+ T cell lines were prepared using splenocytes from DO11.10 T cell receptor (TCR) transgenic mice that express an OVA-specific TCR transgene (25). Equal numbers of T cells and antigen presenting cells (mitomycin c–treated and T cell–depleted BALB/c splenocytes) were incubated with 1 μg OVA peptide (p56lck– and IL-4–deficient T cells (Fig. 2C) and could be specifically blocked by the addition of CTLA-4 immunoglobulin during immunoprecipitation (4, 6).

The interaction of CTLA-4 with TCRζ in activated T cells is likely to be complex and may require additional T cell–specific proteins. Therefore, we examined the CTLA-4–TCRζ association in a non–T cell transfection system. Human embryonic kidney epithelial (293) cells were transiently transfected with a plasmid containing murine TCRζ and one encoding murine CTLA-4. The 16-kD TCRζ chain was coprecipitated with CTLA-4 (Fig. 3A). The TCRζ association was specific as mAb to CTLA-4 did not precipitate the 16-kD protein from cells transfected with vector alone or with a truncated form of CTLA-4 lacking the cytoplasmic tail. The importance of the CTLA-4 tail in the TCRζ interaction was confirmed by coexpressing a construct...
Requirement for IL-13 Independently of IL-4 in Experimental Asthma

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