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Importance of Cytokines in Murine Allergic Airway Disease and Human Asthma[1]

Fred D. Finkelman[*,†,‡], **Simon P. Hogan**[§], **Gurjit K. Khurana Hershey**[¶], **Marc E. Rothenberg**[§], and **Marsha Wills-Karp**[‡]

[*]Department of Medicine, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH 45220

[†]Division of Immunology, University of Cincinnati College of Medicine, Cincinnati, OH 45267

[‡]Divisions of Immunobiology, Cincinnati, OH 45229

[§]Allergy, and Cincinnati, OH 45229

[¶]Asthma Research Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229

Abstract

Asthma is a common, disabling inflammatory respiratory disease that has increased in frequency and severity in developed nations. We review studies of murine allergic airway disease (MAAD[2]) and human asthma that evaluate the importance of Th2 cytokines, Th2 response-promoting cytokines, IL-17 and pro- and anti-inflammatory cytokines in MAAD and human asthma. We discuss murine studies that directly stimulate airways with specific cytokines or delete, inactivate, neutralize or block specific cytokines or their receptors, as well as controversial issues, including the roles of IL-5, IL-17 and IL-13Rα2 in MAAD and IL-4Rα expression by specific cell types. Studies of human asthmatic cytokine gene and protein expression, linkage of cytokine polymorphisms to asthma, cytokine responses to allergen stimulation and clinical responses to cytokine antagonists are discussed as well. Results of these analyses establish the importance of specific cytokines in MAAD and human asthma and have therapeutic implications.

Introduction

Atopic asthma is an inflammatory respiratory disorder that, along with other allergic conditions, has more than doubled in prevalence and severity in developed countries during the past 60 years. Atopic asthma is common; approximately 34.1 million Americans develop asthma during their lifetime and approximately 70% of individuals with this diagnosis have allergies (1, 2). A great deal has been learned about the pathogenesis of asthma during the past 30 years and much of this new knowledge relates to the roles of cytokines in asthma pathogenesis. Inhalation of allergens stimulates both bone marrow- and non-bone marrow-derived cells of the innate immune system to secrete cytokines that promote antigen

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[2]Abbreviations: AHR, airway hyperresponsiveness; FEV1, volume of air expelled during the initial second of forced expiration; GCH, goblet cell hyperplasia; i.n., intranasal; i.t., intratracheal; MAAD, murine allergic airway disease.

Corresponding Author: Fred D. Finkelman, Phone: 513 636-6656; FAX: 513 636-6657; ffinkelman@pol.net.

presentation to $CD4^+$ T cells and influence both antigen-presenting cells and the T cells themselves in a way the promotes a Th2 response (3). Th2 cytokines — IL-4, IL-5, IL-9 and IL-13 (4) — then induce the changes in the airways and lung parenchyma that are associated with asthma: airway eosinophilia, pulmonary lymphocytosis and mastocytosis, alternative macrophage activation, epithelial cell proliferation with goblet cell hyperplasia (GCH) and increased mucus secretion, smooth muscle hyperplasia, hypertrophy and hypercontractility, subepithelial fibrosis, IgE secretion, increased production of chemokines that attract T cells, eosinophils, neutrophils and mast cells or their precursors to the lungs, and airway hyperresponsiveness (AHR, defined as increased sensitivity to agents, such as cholinergic agents and other stimuli that cause smooth contraction that increases airway resistance by narrowing airways) (4, 5). Together, these changes in airway structure and function result in the clinical picture of asthma: episodic difficulty in breathing with wheezing and/or coughing that is caused by reversible airway obstruction and is ameliorated by inhalation of β-adrenergic agonists.

Cytokine roles in murine allergic airway disease

The importance of Th2 cytokines

Experiments performed largely in mice have provided a consensus view of cytokine roles in asthma pathophysiology that stresses the importance of the Th2 cytokines. IL-4 and IL-13 stimulate multiple features of asthma (Table I) by binding and signaling through specific receptors; IL-4 binds to both the type I and type II IL-4Rs while IL-13 binds selectively to the type II IL-4R. Both IL-4Rs signal through IL-4Rα, which activates the transcription factor, Stat6 (6). Each IL-4R additional contains a second polypeptide that is required to activate IL-4Rα chain: the cytokine receptor common γ chain (γ_c) for the type I IL-4R and IL-13Rα1 for the type II IL-4R. Because both IL-4 and IL-13 bind to the type II IL-4R, there are probably no unique IL-4R-mediated effects of IL-13, while selective binding of IL-4 by the type I IL-4R and the expression of γ_c but not IL-13Rα1 by some bone marrow-derived cells, including T cells, most B cells (in the mouse) and mast cells, accounts for stimulation of these cell types by IL-4 but not IL-13 (6). Studies with mice deficient in IL-13Rα1 demonstrate that signaling through the type II IL-4R is required to induce GCH and AHR, but may be less important than signaling through the type I IL-4R for induction of airway eosinophilia (7, 8). IL-13 is more important than IL-4 for induction of GCH, AHR and chronic remodeling changes, including smooth muscle hyperplasia and subepithelial fibrosis (9, 10), even though either cytokine can stimulate all of these features (11-13). The considerably higher lung levels of IL-13 than IL-4 in murine allergic airway disease (MAAD) (8) probably account to a large extent for the predominant role of IL-13, although type I IL-4R-mediated IL-4 induction of IL-10 and IFN-γ (14), which can inhibit AHR and GCH (15, 16), may also contribute. Differences in the binding of IL-4 and IL-13 to the type II IL-4R most likely also contribute to the dominant role of IL-13 in AHR and GCH induction: IL-4 initially interacts with the type II IL-4R by binding with relatively high affinity to IL-4Rα; the IL-4/IL-4Rα complex then recruits IL-13Rα1 to form the signaling complex. In contrast, IL-13 initially binds to IL-13Rα1 with relatively low affinity; the resulting complex then binds IL-4Rα to form the signaling complex. The higher affinity of the initial binding step for IL-4 than IL-13 appears to allow low concentrations of IL-4 to

signal more effectively than low concentrations of IL-13, while the higher cell membrane concentration of IL-13Rα1 than IL-4Rα appears to allow high concentrations of IL-13 to signal more strongly than IL-4 through the type II IL-4R receptor (17, 18).

In contrast to the greater role of IL-13 than IL-4 in inducing and maintaining AHR, GCH and airway remodeling, both IL-4 and IL-13 appear to contribute importantly to alternative macrophage and dendritic cell activation (macrophages and dendritic cells express both γ_c and IL-13Rα1 and thus, both IL-4Rs) (19-21) and IL-4 has a greater role than IL-13 in the induction of airway eosinophilia (8, 10, 12). The reason for IL-4's stronger stimulation of airway eosinophilia is presently unclear, because both IL-4 and IL-13 signal through the type II IL-4R to induce production of chemokines, including eotaxin-1 (CCL11) and eotaxin-2 (CCL24), which attract eosinophils to the lungs (8). IL-4 effects on other cell types, such as vascular endothelial cells, or on eosinophils themselves that may respond primarily through the type I IL-4R, may account for the difference. Expression of γ_c, but not IL-13Rα1 by most murine B cells also accounts for the unique requirement for IL-4, in mice, for induction of IgE responses to T cell-dependent Ags (8, 22, 23). The most critical role of IL-4 in allergic airway disease, however, is in induction of the Th2 cytokine response. This role is not shared by IL-13, because T cells express γ_c but not IL-13Rα1 (24, 25). Although IL-4 is not an absolute requirement for naïve T cell differentiation into Th2 cells (26), IL-4-induced Stat6 stimulation of GATA3, the transcription factor required for Th2 differentiation (27), amplifies Th2 differentiation sufficiently to be required in many instances for the development of a predominant Th2 response (28); this requirement has been observed in most, but not all mouse models of asthma (29-35). Consistent with this, the presence of supernormal concentrations of IL-4 allows the generation of Th2 responses to Ags administered via the airways in an otherwise tolerogenic manner, suggesting that airway IL-4 responses to one Ag probably increase the risk of developing allergic responses to other inhaled Ags (36).

The importance of IL-4 and IL-13 in the induction and maintenance of murine allergic airway disease have been demonstrated in several ways: 1) induction of key features of allergic airway disease by intranasal (i.n.) or intratracheal (i.t.) administration of either cytokine (8, 9, 12, 37); 2) transgenic overexpression of either cytokine in airway epithelial cells (11, 13); 3) suppression of allergen-induced allergic airway disease by administration of neutralizing mAbs to IL-4 or IL-13 (33, 38), soluble IL-4Rα (31) or soluble IL-13Rα2 (9, 10), a blocking anti-IL-4Rα mAb (39), or a mutant IL-4 that acts as an IL-4R antagonist (40, 41); 4) genetic deletion of IL-4 (42, 43), IL-13 (44), IL-4Rα (8) or IL-13Rα1 (7, 8); or 5) suppression of one of these molecules with anti-sense DNA (45). Results differ in the above-cited papers, depending on the precise allergen, immunization schedule, mouse strain and inhibitory procedure employed. However, with a few exceptions, inhibition of IL-4 suppresses the development of a pulmonary Th2 response and allergic airway disease as well as already established airway eosinophilia and IgE production, but does not affect established AHR or GCH (33); inhibition of IL-13 can suppress even established AHR and GCH but has less effect on eosinophilia or IgE production (10); absence of IL-13Rα1 prevents AHR and GCH but has little effect on the development of an IgE response and only modestly prevents development of eosinophilia (8) and inhibition of IL-4Rα suppresses all features of even established allergic airway disease with the exception of mastocytosis (45).

However, currently available anti-IL-4Rα mAbs have been less effective than direct IL-13 antagonists at suppressing GCH and AHR, most likely because these anti-IL-4Rα mAbs do not remove cell membrane IL-4Rα and are less effective at blocking IL-4Rα signaling by IL-13 than by IL-4 (F. Finkelman, unpublished data).

Although IL-4 and IL-13 are generally the cytokines accorded primacy in the induction and maintenance of allergic airway disease, the consensus view also confers importance on IL-5 and, to a lesser extent, IL-9. There is general agreement that IL-5 is critical for stimulating eosinophil development, survival, activation and response to other cytokines, including the eotaxins (46, 47). The importance of airway eosinophils in the induction and maintenance of the airway Th2 response, AHR and GCH is debated and may be mouse strain- and allergen-dependent (see section on controversies, below); however, IL-5-dependent eosinophils are generally agreed to make an important contribution to asthmatic airway remodeling, especially sub-epithelial fibrosis (48, 49).

Airway overexpression of IL-9 can induce the full allergic airway disease phenotype, including eosinophilia, GCH and AHR (50); however, these effects result primarily from IL-9 induction of increased IL-5 and IL-13 secretion by non-T cells (51) and IL-9 has not been found to be important in most studies of MAAD (52), although there is one exception (53). IL-9 does, however, directly promote airway mastocytosis (54) and migration of mast cell precursors to the lungs; an effect not shared by IL-3, IL-4, IL-5, or IL-13 (55).

Cytokines that stimulate allergic airway disease by promoting a Th2 response

Airway over-expression of other cytokines, including IL-25 (also called IL-17E), IL-33 and thymic stromal lymphopoietin (TSLP) induces and promotes allergic airway disease indirectly by stimulating production of IL-4, IL-5 and/or IL-13 (29, 56, 57). Unlike IL-9, which is produced by T cells, mast cells and basophils, allergen stimulation of epithelial cells appears to be important for the initial production of IL-25 (58), IL-33 (3) and TSLP (59). Each of the 4 cytokines that promote allergic airway disease indirectly by promoting IL-4, IL-5 and/or IL-13 secretion has been shown to be important in at least some mouse models of asthma in studies in which the cytokine or its receptor was blocked by inhibitory proteins or deleted genetically (53, 60-62). In addition to direct effects on T cells that can promote Th2 cytokine production, IL-9 and IL-33 stimulate non-T cells to secrete Th2-associated cytokines (51, 57, 63) and TSLP stimulates dendritic cells to express the Th2 differentiation-promoting co-receptor, OX40 ligand (64). IL-25 has also been reported to promote AHR independently of its stimulatory effects of Th2 cytokine secretion; neutralization of IL-25 when already sensitized mice were exposed to aerosolized Ag suppressed AHR without influencing airway inflammation or Th2 cytokine production and inhaled IL-25 induced AHR in mice genetically deficient in IL-4, IL-5, IL-9 and IL-13 (60).

IL-25, IL-33 and TSLP are not the only cytokines implicated in Th2 response induction. AHR, Th2 cytokine production and IgE levels are significantly reduced in allergen-immunized IL-1α/IL-1β-deficient mice and increased in IL-1R antagonist-deficient mice (65). Similarly, GM-CSF promotes development of a Th2 response, even in the absence of IL-4 (66). The GM-CSF contribution to AAD is mediated, at least in part, by stimulating activation, airway migration and proliferation of myeloid dendritic cells that can present Ag

in a way that promotes Th2 differentiation (67). However, although GM-CSF deficiency or neutralization can inhibit diesel exhaust particle-induced AHR (68) and allergen-induced development of GCH, airway eosinophilia and IL-5 production (69), it has not always inhibited allergen-induced IL-4 or IL-13 production or AHR (69).

The effects of the IL-1 family cytokine, IL-18, on Th2 cytokine production and MAAD are more complex. Genetic deficiency of IL-18 has been reported to exacerbate (70) or inhibit (71) different MAAD models and the effects of airway IL-18 inoculation on MAAD vary and depend on time and route of IL-18 relative to allergen administration. This variability most likely reflects the different effects of IL-18 when it interacts with different cytokines; specifically, IL-18 enhances IL-12 induction of a Th1 response, IL-2 induction of a Th2 response and IL-3 induction of Th2 cytokine production by mast cells and basophils (72).

Cytokine suppression of allergic airway disease

Not all cytokines promote allergic airway disease; IL-12, type I and type II IFNs and the "anti-inflammatory" cytokines, IL-10 and TGF-β, suppress this disorder (15, 16, 73-80), although there are caveats to this generalization that probably reflect the pleomorphic effects of each of these cytokines. Endogenously produced IL-12p40, a component of IL-12 and IL-23, is required to suppress AHR and peribronchial fibrosis, but not airway eosinophilia, in a chronic allergen administration model of allergic disease (81) and treatment with IL-12 can suppress even established allergic airway disease (76). The suppressive effects of IL-12 depend partially on IL-12 induction of IFN-γ (76) and treatment with large doses of IFN-γ or type I IFN can also suppress at least some features of allergic airway inflammation, especially eosinophilia, in worm infection models (80). Consistent with this, IFN-γ deficiency has been reported to increase the duration of eosinophilia in allergen-immunized mice (82). Mice deficient in T-bet, the transcription factor required for Th1 responses, spontaneously develop allergic airway disease (83) that is IL-13-dependent (84). In contrast to these observations, AHR was induced to the same extent when naïve mice were inoculated with both Th1 and Th2 cells plus the appropriate Ag as when they were inoculated with only Th2 cells plus Ag (85). Even more surprisingly, adoptive transfer of eosinophils into the lungs of SCID mice has been reported to induce IFN-γ-dependent AHR (86) and transgenic IFN-γ expression in mouse lung has been reported to induce increased IL-5 and IL-13 production and airway eosinophilia (87). Although one may speculate that low levels of IFN-γ may promote allergic airway disease by increasing Ag presentation and inflammatory cell recruitment while higher levels of IFN-γ suppress Th2 responses and Th2 cytokine effects, the specific conditions that determine the net effect of IFN-γ on allergic responses in the lung and other organs remain to be determined.

The importance of IL-10 as an allergy-limiting cytokine is supported by observations that IL-10 treatment suppresses AHR, GCH and airway eosinophilia, that anti-IL-10 or anti-IL-10R mAb treatment has the opposite effect in most studies (16, 73, 88, 89), and that suppression of AHR by regulatory T cells is IL-10-dependent (90). Surprisingly, however, AHR has been difficult to induce in IL-10-deficient mice (91). This apparent discrepancy has recently been shown to reflect IL-10 suppression of IL-13Rα2, a soluble and cell membrane protein that can act as an IL-13 antagonist by binding IL-13 without inducing

pro-allergic signaling (92). Consequently, mice deficient in both IL-10 and IL-13Rα2 develop more severe allergic airway disease than mice deficient in either (92). MAAD is also suppressed by another cytokine associated with regulatory T cells, TGF-β (73, 79). Chronic TGF-β treatment, however, may have the risk of enhancing development of airway smooth muscle hyperplasia and pulmonary fibrosis (93, 94).

Controversies in cytokine involvement in MAAD

The role of IL-5 in murine AAD

The importance of IL-5 and the eosinophil, which is predominantly IL-5-dependent, for induction and maintenance of the main features of MAAD, other than airway remodeling, very likely depends on the mouse strain studied, the allergen and precise immunization protocol used and possibly the local bacterial flora and animal husbandry practices. Without considering these variables, it is impossible to draw straightforward conclusions from the copious literature. One group that used a GATA1 mutation to prevent production of mature eosinophils found that these cells contribute importantly to the generation of a Th2 response in C57BL/6 mice by producing or promoting production of chemokines that recruit T cells that subsequently produce a Th2 response; however, eosinophils were not required for this purpose in similarly immunized BALB/c mice (95, 96). Consistent with this strain dependency, several reports have described an IL-5 requirement for GCH and AHR in C57BL/6, but not BALB/c mice (30, 32, 33, 44, 97, 98). Also consistent with the concept that IL-5 promotes allergic responses indirectly by promoting a Th2 response, the induction of GCH by transgenic pulmonary IL-5 overproduction has been reported to be $CD4^+$ T cell and IL-4-dependent (99). However, intravenous IL-5 reconstituted AHR and airway eosinophilia in allergen immunized mixed background C57BL/6 – 129 mice that were Stat6-deficient, suggesting that IL-4 and IL-13 were not required (100) (Stat6 is required for IL-4/IL-13-induced AHR), and two groups have reported anti-IL-5 mAb suppression of AHR in BALB/c mice (101, 102). Endogenously produced IL-5 has also been reported to allow the development of AHR in allergen-immunized IL-4-deficient mice (103) and even to allow the development of IL-13-dependent AHR in IL-4Rα-deficient mice (through an unknown mechanism) (104). The safest conclusions to draw from these observations are that: 1) eosinophils and IL-5 contribute more to AHR and GCH in C57BL/6 mice than in BALB/c mice; and 2) very robust allergen immunization procedures and/or environmental features may induce redundant mechanisms that bypass Stat6 and IL-4Rα requirements that are seen under more typical circumstances.

The role of IL-17 in murine AAD

Because IL-17A and IL-17F potently induce CXC chemokines and neutrophil responses, among their multiple effects (105, 106), it is reasonable to expect IL-17A and IL-17F to be involved in the airway neutrophilia that characterizes many mouse models of asthma. Indeed, IL-17A and IL-17F have been reported to stimulate airway neutrophilia and have additional important effects in MAAD; however, these additional effects have varied considerably in different studies. IL-17RA-sufficient, but not IL-17RA-deficient mice (which fail to respond to IL-17A, IL-17F and IL-17E/IL-25 (107, 108)) develop MAAD when sensitized with ovalbumin and subsequently challenged i.n. with the same Ag (109).

Failure of the IL-17RA-deficient mice to develop MAAD may have reflected a lack of responsiveness to IL-17E rather than IL-17A or blocking of both IL-17A and IL-17F, which have similar effects. This possibility is supported by a study in which ovalbumin immunization induced the development of airway inflammation and AHR to the same extent in IL-17A-deficient and sufficient mice that had a mixed genetic background (110). IL-17A neutralization that was restricted to the time of i.n. ovalbumin challenge exacerbated airway eosinophilia and AHR in C57BL/6 mice in one study, while IL-17A administration had the opposite effects (109). However, in a different study, i.t. administration of IL-17A immediately after challenge of ovalbumin-sensitized C57BL/6 mice with aerosolized ovalbumin exacerbated MAAD, including AHR (111). Induction of AHR by inoculation with IL-17A was not replicated by inoculation of IL-17F in this study and required both neutrophils and the presence of Th2 cytokines. In contrast, pulmonary transduction of BALB/c mice with the gene for IL-17F was reported to increase AHR and to exacerbate AHR induced by ovalbumin sensitization and challenge (112). In yet another study performed with a BALB/c - ovalbumin variant of MAAD, neutralization of IL-17 at the time of ovalbumin challenge inhibited airway neutrophilia and exacerbated airway eosinophilia but had little effect on AHR (113). In contrast, neutralization of IL-17 at the time of antigen challenge in another BALB/c - ovalbumin MAAD study suppressed airway neutrophilia, eosinophilia and AHR (114). More studies are required to determine the reasons for the differences reported in these papers and to evaluate the implications of these results for human asthma.

Our own observations, however, suggest that some of the variability in the effects of IL-17 in MAAD is mouse strain-related. We find that considerable pulmonary IL-17A is produced when MAAD is induced in A/J mice, which are particularly susceptible to allergen inoculation, while little or no pulmonary IL-17A if produced when MAAD is induced in C3H mice, which are resistant to this disease. Neutralization experiments demonstrate that IL-17A synergistically enhances IL-13-dependent AHR in A/J mice, while, not surprisingly, neutralization of IL-17A has little or no effect on MAAD in C3H mice (M. Wills-Karp, submitted). This variability may be relevant to humans, inasmuch as particularly high IL-17A concentrations are found in the lungs of people who have severe asthma with large numbers of BAL neutrophils (115, 116).

The role of IL-13Rα2 in MAAD

In addition to binding to IL-13Rα1 with low affinity and subsequently forming a high affinity association with an IL-13Rα1/IL-4Rα signaling complex, IL-13 binds with high affinity to IL-13Rα2 (117). In the mouse, IL-13Rα2 exists in two forms, a soluble form present normally in serum in low ng/ml concentrations and a cell membrane form that is expressed by smooth muscle and possibly other cell types (118, 119 and G. K. Khurana Hershey, unpublished data). These two forms are generated predominantly by alternative mRNA splicing, although proteolytic cleavage of the membrane form can generate small amounts of the soluble form (111). IL-13Rα2 has been found in several experimental systems to be a potent IL-13 antagonist; mice that lack a functional IL-13Rα2 gene generally develop more severe IL-13-mediated pathology (120-122). One group, however, has reported a signaling pathway by which an IL-13 interaction with membrane IL-13Rα2

can promote TGF-β production and pulmonary fibrosis (94) and another has reported that complexes of IL-13 and soluble IL-13Rα2 have a long in vivo half-life and promote expression of two genes; one associated with exacerbation of oxidative inflammation and the other associated with increased activation of inflammatory and antigen presenting cells (118). Neither mechanism, however, activates Stat6, which is required for IL-13-induction of GCH and AHR (123), and IL-13Rα2-deficient mice are reported to develop more severe MAAD than wild-type mice following allergen inoculation (124). Surprisingly, we find that this is not always the case; some allergen administration protocols at least initially induce disease that is more severe in wild-type than in IL-13Rα2-deficient mice (G. K. Khurana Hershey and M. Wills-Karp, unpublished data). It is not known if this reflects one of the two mechanisms noted above or, possibly, generation of an IL-13Rα2-bound IL-13 pool at the cell membrane that can then be transferred to the type II IL-4R. Additional studies are required to evaluate these possibilities and determine how they influence asthma in humans, who express only the membrane isoform of IL-13Rα2 (125, 126). Indeed, the difference in IL-13Rα2 expression between mouse and man suggests that this molecule may function differently in these two species and raises the possibility that these species may also have differences in IL-13 function.

Cells directly involved in IL-4Rα-mediated AHR

Although multiple cytokines act on multiple cell types to induce the full features of MAAD, hypotheses about how cytokines induce AHR have focused predominantly on IL-13, epithelial cells and smooth muscle cells. The focus on IL-13 is explainable by its ability to directly induce AHR and on its requirement in most studies of allergen-induced AHR (9, 10). Smooth muscle and epithelial cells have been implicated by in vitro studies demonstrating that IL-13 can act directly on smooth muscle to increase its contractility (127-136) and in vitro and in vivo demonstrations that IL-13 directly induces epithelial cell hyperplasia and GCH (124, 137, 138), which narrow airways, so that a given contraction by airway smooth muscle will induce a greater than normal increase in airway resistance (139). The importance of the IL-13 – epithelial cell axis was illustrated by demonstration that AHR develops in mice that overproduce IL-13 in their lungs and express Stat6 only in airway epithelium (124); however, AHR was also induced by IL-13 in mice that selectively lack IL-4Rα in airway epithelial cells (137). This indication that at least one additional cell type must contribute to IL-13-induced AHR recently led to studies with mice that express IL-4Rα only on smooth muscle or on all cell types other than smooth muscle (F. Finkelman, unpublished data). Studies with these mice demonstrate that direct IL-4 and IL-13 effects on smooth muscle, like airway epithelium, are sufficient but not necessary to induce AHR and support the use of the mouse as an appropriate model for studying smooth muscle contributions to asthma pathology. Additional studies are required to determine if IL-13-induced AHR can be totally accounted for by its effects on epithelial and smooth muscle cells.

Applicability of murine studies to human asthma

MAAD is an imperfect model of human asthma and allergy-related effector and regulatory immune mechanisms in mouse and man are usually similar in general but can differ in important details (140). Consequently, while cytokine studies with MAAD can be used to

make predictions about cytokine roles in human asthma and to investigate mechanisms by which cytokines may promote or inhibit asthma pathogenesis, human studies must be performed to confirm or refute hypotheses generated in the mouse. When comparing the results of mouse and human studies, however, it is important to consider differences in the questions being addressed; for example, most murine cytokine neutralization studies investigate whether a specific cytokine is important in MAAD induction, while human cytokine neutralization studies always evaluate individuals who already have asthma and, thus, study importance of disease maintenance rather than induction. It is likely that some cytokines are more crucial for asthma induction than for maintaining established disease.

Cytokine roles in human asthma

Specific cytokines have been associated with human asthma through 4 types of studies: 1) comparison of levels of cytokine gene expression or protein in blood, exhaled breath condensates, or BAL or sputum cells between asthmatics and non-asthmatics; 2) comparison of the allele frequency of polymorphic cytokine genes between asthmatics and non-asthmatics or severe vs. less severe asthmatics; 3) determination of cytokine production following installation of allergens into bronchi; and 4) determination of the clinical effects of cytokine neutralization or cytokine receptor blocking on established asthma.

Comparison of cytokine expression by asthmatic and non-asthmatic individuals

Although variable results have been reported in studies that correlate cytokine production and cytokine gene expression in blood or BAL or sputum cells with asthma, most human studies associate asthma with increased gene expression and secretion of IL-4 (141-149) and IL-5 (141, 143-145, 150) and some provide similar data for IL-3 (151, 152), IL-9 (153), IL-13 (146, 152), GM-CSF (151, 152), or Stat6 (154). In contrast, as was true for mice, some human studies suggest a positive, and some a negative association between asthma and airway production of IFN-γ (147-149, 152, 155, 156). In addition, two studies suggest that IL-18 levels are lower in airway secretions of asthmatic individuals than in non-asthmatics (157, 158).

Genetic polymorphisms linked to asthma

Approximately 100 studies have been published that link increased frequency or severity of asthma to cytokine gene or cytokine signaling gene polymorphisms. More than 10 studies have linked asthma frequency or severity to polymorphisms in genes that encode IL-4 (159-168), IL-13 (162, 169, 170), TNF (159, 171-177) and IL-4Rα (18, 162, 165, 168, 178-181). Several studies have also linked asthma to genes that encode the IL-1 receptor antagonist (IL-1RA) (182-184), IL-10 (185-189), IL-18 (190-194), IFN-γ (195-197), TGF-β1 (178, 185, 186, 198-202) and Stat6 (162, 203), while polymorphisms in genes that encode IL-1β (182), IL-2 (186), IL-6 (183), IL-9 (204), IL-12/27p40 (205, 206), IL-15 (207), IL-17F (208), IL-21 (209), IL-27p28 (210), LT-α (211), TSLP (212), TGF-β2 (213) and Stat4 (196) have been linked to asthma frequency or severity by fewer studies (214). Some of these studies link asthma risk to a single nucleotide polymorphism (SNP) in a cytokine gene exon (18), suggesting that polymorphic variants influence cytokine function

or longevity, while other studies link asthma risk to a SNP in a cytokine promoter (164), suggesting that polymorphic variants influence cytokine production. Several polymorphism studies have identified combinations of allelic variants of different genes that together appear to additively or synergistically influence the risk of asthma; these include combinations of allelic variants of the genes that encode TNF and IL-13 (172), IL-10 and TGF-β (185), IL-4Rα and IL-9R (215), Stat4, Stat6 and IFN-γ (196), IL-13 and IL-4Rα (169, 201) and IL-4, IL-13, IL-4Rα and Stat6 (162). Studies that fail to demonstrate linkage to asthma have also been published for cytokine or cytokine gene polymorphisms, including IL-1β (189), IL-4 (179), IL-12/IL-23p40 (216), IL-16 (160, 217), IL-17F (218), TGF-β1 (219, 220), IL-18 (221), TNF (222), IL-4Rα (222), Stat4 (223) and Stat6 (223).

Positive linkage associations do not necessarily indicate that a specific cytokine or cytokine signaling molecule is involved in asthma pathogenesis; the gene studied may instead be associated by linkage disequilibrium with a polymorphic variant of a different gene that is more directly involved. Negative studies also are not conclusive; they may have investigated the “wrong” polymorphic variant of a gene that really is involved in asthma pathogenesis, a specific racial or ethnic group in which polymorphic variants of the gene studied are not risk factors for asthma, or too few patients to identify a genuine association. Additionally, some SNP studies that link specific cytokines to asthma report linkage only for individuals with exposure to specific environmental factors, such as dust mite allergen (224, 225), freeway traffic (202) or tobacco smoke (222).

Relatively few studies demonstrate a mechanism that explains how a cytokine or cytokine-related polymorphism can influence asthma frequency or severity; exceptions include demonstration of an IL-4 promoter polymorphism that appears to increase asthma frequency by increasing IL-4 production (226), an IL-13 polymorphism that appears to exacerbate asthma by enhancing IL-13 activation of Stat6 and decreasing IL-13 affinity for IL-13Rα2 (169, 227); an IL-17F polymorphism that protects against asthma by antagonizing wild-type IL-17F activity (208); an IL-18 polymorphism that appears to increase asthma severity by increasing IL-18 expression (228) and an IL-4Rα polymorphism that increases asthma severity by promoting signaling pathways that synergize with Stat6 activation to induce genes that contribute to allergic inflammation (18).

Effects of allergen and cytokine challenge

Although bronchoscopic studies in which in vivo cytokine production by a lung segment is evaluated after allergen challenge of that lung segment have provided variable results, increased gene expression or secretion of IL-4, IL-5, IL-13 and GM-CSF have been reported by most studies (229-233). Consistent with this and with mouse studies, inhalation of recombinant human IL-4 induced AHR and sputum eosinophilic within 24 hours (234). Inhalation of recombinant human IL-5 by Chinese mild asthmatic subjects was also reported to induce AHR and airway eosinophilia in one study (235); however, these observations were not reproduced in a two studies in which British mild asthmatic subjects inhaled the same or a larger dose of recombinant human IL-5 from the same source (236, 237).

Clinical trials

Because individuals come to clinical attention only after they develop symptoms of disease, the most practical clinical question relating cytokines and asthma is whether a particular cytokine or cytokine receptor is involved in maintaining, rather than inducing asthma. Although in vivo neutralization studies with cytokine or cytokine receptor antagonists provide the most definitive way to evaluate the importance of a cytokine in maintaining established asthma, only a relatively small number of these studies have been reported and some of these have limitations that make them difficult to interpret.

Studies that administered soluble IL-4Rα as an IL-4 antagonist initially showed some promise of increasing asthma control (238), but this failed to be replicated by a later, larger study (239). Initial clinical trials of anti-IL-5 mAb in asthma patients showed considerable decreases of blood eosinophilia, a partial decrease in lung eosinophilia and no beneficial effects on lung function or symptoms (240, 241), but appeared to have a beneficial effect on remodeling by decreasing deposition of extracellular matrix proteins (242). More recent studies that have evaluated anti-IL-5 mAb effects in more defined patient populations have provided more impressive results: intravenous injection of anti-IL-5 mAb increased the amount of air expelled during the initial second of forced expiration (FEV1) and decreased asthma exacerbations, steroid requirement and blood and sputum eosinophilia in patients with steroid-resistant asthma with sputum eosinophilia in one study (243), and decreased severe exacerbations and blood and sputum eosinophilia and increased quality of life without increasing FEV1 or decreasing symptoms or AHR in a second study (244).

Treatment with either of 2 TNF antagonists was reported to induce a statistically significant beneficial effect: an increase in asthma control in one study (245), a decrease in asthma exacerbations in a second study (246) and decreased AHR with increased FEV1 and asthma-related quality of life in the third study (247). However, the beneficial effects were different for the three studies and were relatively small.

Perhaps the most impressive observations have been made in a phase 2a trial of pitrakinra, a mutated recombinant human IL-4 that blocks IL-4 and IL-13 effects by binding to IL-4Rα without signaling. Pitrakinra inhalation substantially decreased the allergen-induced decrease in FEV1 and accelerated the recovery from this effect of allergen inhalation (248). Phase 2b studies of inhaled pitrakinra in asthmatics are reported to be in progress.

Undoubtedly, the small number of reports of clinical trials of cytokine or cytokine receptor antagonists reflects the high cost of such studies and other economic considerations; however, it is also likely that additional studies have been performed, but not reported because of negative results. In this regard, it needs to be appreciated that the results of human trials, like animal studies, can be misleading. It is understandable, but unfortunate that maximum doses of cytokine or cytokine receptor antagonists in many human trials may be determined by economic rather than biologic considerations and that most trials are not set up to determine the extent to which a targeted cytokine or cytokine receptor is blocked in the lungs. Consequently, it can be impossible to determine whether negative results of a clinical trial reflect lack of importance of the targeted molecule in the maintenance of human asthma or inadequate blocking of the target. Similarly, clinical trials with cytokine

antagonists do not always investigate whether the antagonist eliminates the cytokine or forms a soluble complex with the cytokine that may prolong its in vivo half-life and allow agonist effects when the complex dissociates (249, 250). In the same vein, clinical trials with cytokine receptor antagonists don't always investigate the effect of the agent on cell membrane expression of the targeted receptor, although removal of the receptor would likely have a better inhibitory effect than simple receptor occupancy and increased expression of the receptor might be deleterious. It would seem advisable for future clinical trials to address these issues when possible.

Conclusions

Data from both murine and human studies support the importance of Th2 cytokines and, to a lesser extent, inflammatory cytokines produced by the innate immune system, in MAAD/asthma development and maintenance. These same data, however, demonstrate that murine strain differences and differences in the allergens used to induce MAAD and the protocols used to administer these allergens all influence the importance of a particular cytokine in MAAD induction and maintenance. Other environmental influences, such as animal husbandry practices and variations in "normal" bacterial flora, may also affect the role of a particular cytokine in murine AAD. Similar factors are likely to influence the importance of a particular cytokine in human asthma, as shown by differences in the association of cytokine gene polymorphisms with asthma in different ethnic and racial groups and by the different outcomes of anti-IL-5 mAb therapy in patients whose asthma had different clinical characteristics. Taken together, mouse and human studies presently suggest that therapies that effectively suppress IL-13 or IL-13 along with IL-4 and, possibly, other Th2 cytokines may offer the best cytokine-based approach for suppressing *established* asthma, with the caveats that no single therapy is likely to be effective for all individuals with this disease and that different cytokine-based therapies are likely to prove most effective for different groups of asthmatic individuals. We believe that identification and validation of cytokine, cytokine receptor, and cytokine-associated signaling molecules that are appropriate therapeutic targets will require additional mouse studies, particularly studies of molecules involved in maintenance of established MAAD, as well as clinical trials that evaluate mechanisms in addition to toxicity and efficacy.

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Table I

Cytokines that directly promote features of asthma

Feature	Cytokines Implicated
Eosinophilia	IL-4, IL-5, IL-13
Goblet Cell Metaplasia	IL-4, IL-13
Airway Hyperresponsiveness	IL-4, IL-13, IL-17A
IgE Production	IL-4, IL-13
Mastocytosis	IL-3, IL-9
Alternative Macrophage Activation	IL-4, IL-13
Smooth Muscle Remodeling	IL-4, IL-13
Th2 Induction/Maintenance	IL-4, IL-9, IL-17E (IL-25), IL-33, TSLP
Subepithelial fibrosis	IL-4, IL-13