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Interleukin-4, Interleukin-13, Signal Transducer and Activator of Transcription factor 6, and Allergic Asthma

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Abstract

Interleukin (IL)-4 and IL-13 share many biological activities. To some extent, this is because they both signal *via* a shared receptor. IL-4R α . Ligand of IL-4R α . results in activation of Signal Transducer and Activator of Transcription factor 6 (STAT6) and Insulin Receptor Substrate (IRS) molecules. In T- and B-cells, IL-4R α . signaling contributes to cell-mediated and humoral aspects of allergic inflammation. It has recently become clear that IL-4 and IL-13 produced in inflamed tissues activate signaling in normally resident cells of the airway. The purpose of this review is to critically evaluate the contributions of IL-4- and IL-13-induced tissue responses, especially those mediated by STATS, to some of the pathologic features of asthma including eosinophilic inflammation, airway hyperresponsiveness, subepithelial fibrosis and excessive mucus production. We also review the functions of some recently identified IL-4- and/or IL-13-induced mediators that provide some detail on molecular mechanisms and suggest an important contribution to host defense.

Keywords

IL-4; IL-13; STAT6; allergy; asthma; inflammation; airway hyperresponsiveness; fibrosis; mucus

IL-4 AND IL-13 SIGNALING

As shown (illustration 1), the cytokines IL-4 and IL-13 activate STAT6 and IRS signaling by heterodimerization of IL-4R α . with one of two other receptor subunits (reviewed in [1]). IL-4 is a ligand of the type I IL-4 receptor composed of IL-4R α and the common γ chain of cytokine receptors. Both IL-4 and IL-13 are ligands of the type II IL-4 receptor composed of IL-4R α and IL-13R α 1. Except for human T-cells and mouse T- and B-cells, which only express the type I IL-4 receptor, most cells express both receptor types. Some cells express the IL-13R α 2 chain which binds IL-13 and is thought to function as a non-signaling decoy receptor [2]. ligation of type I and type II IL-4 receptors results in transphosphorylation of receptor-associated janus kinase (JAK) family members. Specifically, JAK1 is associated with the IL-4R α chain, JAK3 is associated with the common γ chain, and JAK2 or Tyk2 are associated with the IL-13R α 1 chain. Receptor heterodimerization activates the associated

JAKs and consequently phosphorylation of the cytoplasmic tail of IL-4R α ensues at specific tyrosine residues.

The amino acid sequences parenthetic to Tyr⁴⁹⁷ of IL-4R α define a region that is highly homologous with amino acid sequences in the insulin and insulin-like growth factor 1 receptors [3]. This region is referred to as the insulin/IL-4 receptor (14R) motif. Phosphorylation of IL-4R α at Tyr⁴⁹⁷ results in recruitment and phosphorylation of IRS-1 and/or IRS-2 molecules [3-5]. Tyrosine phosphorylated IRS-1 and IRS-2 molecules serve as docking sites for numerous src-homology domain 2 containing enzymes and adaptor proteins resulting in the subsequent recruitment and activation of phosphoinositol 3-kinase (PI3-K) [5-8]. Studies of cell lines transfected with mutant IL-4R chains and IRS-2-deficient lymphocytes suggest that the 14R motif and IRS-2 signaling pathway mediate IL-4-induced mitogenic responses [3,6,9, 10]. In a recent study of mice with a point mutation introduced into the tyrosine site of the 14R motif, it was observed that while mutant CD4⁺ T-cells had abrogated IRS-2 phosphorylation and proliferative responses to IL-4, the mutant CD4⁺ T-cells still had functional STAT6 signaling and were capable of undergoing Th2 differentiation. Even so, mice with the point mutation had more severe experimental allergic asthma responses as compared to wild-type mice, suggesting that there is an overall protective effect of 14R-mediated IRS-2 signaling for the development of allergic airways inflammation [11].

The amino acid sequences surrounding Tyr⁷¹³ of IL-4R α have homology to the immunoreceptor tyrosine-based inhibitory motif (ITIM) [12]. When tyrosine phosphorylated, ITIMs become a docking site for SH-PTPase-containing tyrosine phosphatase-1 (SHP-1) and/or SH-PTPase-containing inositol 5'-phosphatase (SHIP) [13-17]. After docking, these phosphatases are thought to regulate receptor signaling by dephosphorylating activated signaling molecules. Kashiwada and colleagues recently reported that SHP-1, SHP-2, and SHIP can associate with the IL-4R ITIM and that ablation of the IL-4R ITIM resulted in increased proliferative responses to IL-4 with increased activation of STAT6, but not IRS-2 [18]. These results indicate that IL-4R α contains a functional ITIM.

The phosphorylation of IL-4R α at three tyrosine sites (Tyr⁵⁷⁵, Tyr⁶⁰³ and Tyr⁶³¹) is important for the docking of STAT6 monomers [10,19], which then become tyrosine phosphorylated and then disassociate from the receptor and associate with each other to form STAT6 homodimers in the cytoplasm. These translocate to the nucleus and bind to the promoter regions of IL-4 and/or IL-13 responsive genes. Of the various IL-4R α -mediated signaling pathways, the STAT6 signaling pathway has been described as critical for Th2 differentiation [20] and essential for isotype class switching to IgE [21] and thus STAT6 expression is required for the development of experimental allergic asthma in mice [22]. These studies indicate that IL-4 and IL-13, particularly by inducing STAT6 signaling, make important contributions to the initiation of allergic responses. However, both IL-4 and IL-13 are significantly elevated in the airways mucosa of patients with asthma [23-29]. It is therefore believed that their effects on resident cells of the airway are also likely to be of significance to the chronic inflammation and pathologic structural changes, or remodeling, that accompany this disease.

ALLERGIC INFLAMMATION

One important aspect of allergic inflammation in asthma is the migration of Th2 cells and eosinophils into the airway. The Th2 cell supports the influx of eosinophils *via* cytokine secretion. For example, IL-5 is known to provide an important signal supporting the influx of eosinophils into tissues [30]. However, Th2 cells are also important sources of IL-4 and IL-13 that can induce chemokine production by various cells in the airway. For example, IL-4 or IL-13 treatment induces the pro-eosinophilic chemokines eotaxins 1, 2, and/or 3 by cultured airway smooth muscle [31], lung fibroblasts [32], alveolar epithelial cells [33] and vascular endothelial cells [34]. As compared to healthy controls, increased expression of eotaxin 1, 2 and 3 by airway epithelial cells in asthmatics has been reported [35]. An important role for IL-4 and IL-13 effects on epithelial cells in allergic inflammation is supported by *in vitro* studies demonstrating that IL-4 or IL-13 treatment of cultured airway epithelial cells induces chemokines including eotaxins 1, 2 and 3 [35-37] and MCP-1 [38] as well as RANTES, IL-8, gro- α [39] and MIP-3 α [40].

It is clear that IL-4 and/or IL-13 effects on airway epithelial cells result in chemokine expression *in vitro*. However, the *in vivo* evidence is less conclusive. IL-13 treatment directly to the airways of mice results in eotaxin expression by airway epithelial cells [41]. However, in this study IL-13 treatment also induced a small degree of inflammation, therefore epithelial eotaxin expression might have reflected the effects of other mediators. For example, TNF- α is a potent inducer of epithelial eotaxin expression, an effect that is not dependent upon STAT6 binding to the eotaxin promoter but is dependent upon NF- κ B binding to the eotaxin promoter [42]. That IL-13-induced responses in cells other than epithelial cells are required for eosinophilia was suggested by studies of mice in which constitutive transgenic IL-13 production in the airways resulted in induction of chemokines and eosinophilia. However, these chemokine and eosinophilic responses were not induced by IL-13 in STAT6 knockout mice or in STAT6 knockout mice that had STAT6 expression reconstituted exclusively in epithelial cells by expression of transgenic STAT6 under the control of an epithelial cell-specific promoter [43,44]. The observed effects were not mediated by transgenic STAT6 expression alone but required the expression of transgenic IL-13. Further, allergen-induced eosinophilia developed similarly in the lungs of wild-type mice and mutant mice that had conditional IL-4R α deletion limited exclusively to the epithelium [45]. However, it is possible that the allergen exposure protocol used in this study, which induced an acute allergic inflammatory response, was not appropriate for the study of epithelial contributions to the development of eosinophilia.

Still, multiple studies have shown that deletion of STAT6 eliminates the majority of Th2 cells and eosinophils that traffic into the lungs of mice following allergen challenge, independently of its role in Th2 differentiation [46-48]. These studies implicate STAT6 in some resident cell type in the lung that mediates the migration of Th2 cells and eosinophils into the airway. The identity of this cell remains elusive. However, recent studies of chimeric mice generated by reciprocal bone marrow transfers between IL-4R α + and IL-4R α - and IL-4R α $\times$ RAG2 knockout mice (that do not have T- and B-cells) in combination with adoptive transfer of *in vitro* polarized Th2 cells showed that eosinophilic inflammation in the lungs of mice is partially regulated by Th2 cells and also partially

regulated by a bone marrow-derived cell that is not of lymphoid origin but which required expression of IL-4R α and antigen stimulation [49]. This seems to exclude epithelial cells, smooth muscle cells, fibroblasts, endothelial cells, and T- and B-lymphocytes. One potential candidate is the pulmonary dendritic cell although eosinophils, mast cells and monocytes can also fit this description under certain conditions. It remains to be determined whether IL-4R α signaling in dendritic cells contributes to allergic inflammation. However, an important role for IL-4R α signaling in dendritic cells seems plausible as IL-4 and IL-13 regulate the maturation of dendritic cells in the lung [50] and augment the ability of dendritic cells to induce cytokine production by Th2 cells [51].

AIRWAY HYPERRESPONSIVENESS

One of the key characteristics of asthma is the presence of airway hyperresponsiveness (AHR). In humans, AHR is determined by measuring the decline in pulmonary function in response to inhaled broncho-constrictors, typically methacholine. It is sometimes presumed that airway smooth muscle hypercontractility and/or hyperplasia, as it occurs in asthma, underlies the development of AHR. However, the etiology of AHR remains undefined. Methods of inducing and measuring AHR in mice have been developed to help determine causality. Unfortunately, there are major limitations to the relevance of mouse AHR studies. For example, there is no good surrogate in mice for the voluntary forced expiratory maneuver that is central to the measurement of AHR in humans. In mice, AHR is typically measured either by recording changes in air-flow resistance induced by intravenous methacholine during mechanical ventilation or by recording changes in the breathing pattern by plethysmography at times before and after inhalation of methacholine.

Regardless of the method used, it is clear that IL-13 produced during the effector phase of allergic inflammation is a key mediator of AHR in mice [52-55]. However, it was not known whether IL-13 mediates AHR by a direct effect on resident cells in the airway or whether its role was related to its potent pro-inflammatory activity and consequently the downstream activity of other mediators. An important contribution by direct effects of IL-4 and/or IL-13 on airway smooth muscle (ASM) is supported by *in vitro* studies showing that IL-13 can directly increase the contractility of cultured ASM [56] and decrease their relaxation induced by beta-adrenergic agonists [57]. IL-13 augments calcium transients in cultured human ASM cells [58] and augments the calcium and contractile responses of mouse ASM cells [59]. It would be of interest to determine if IL-4 and/or IL-13 effects genetically limited to ASM would lead to the development of AHR *in vivo*.

In addition to the possibility of an important role for IL-4 and/or IL-13-induced ASM responses, there is evidence that the epithelium may be a main target for the development of IL-4 and/or IL-13 induced AHR in mice. For example, mice with STAT6 expression genetically limited to the airway epithelium develop IL-13-induced AHR. This occurred in association with excessive mucus production but independently of eosinophilia [44]. The development of IL-13-induced AHR in the absence of eosinophilia was recently confirmed by Kibe *et al.* but as in the above study, AHR remained associated with excessive mucus production [60]. Both of these results indicate that excessive mucus production might underlie the development of AHR in mice. However, mice with conditional IL-4R α deletion

in epithelium were not protected from allergen-induced AHR even though they were protected from excessive mucus production [45]. Although, this result suggests that AHR and mucus can be regulated independently, it remains to be determined whether excessive mucus production contributes to the development of AHR.

IL-13-induced ST AT6 signaling in epithelium is sufficient [44] but IL-4R α expression by epithelium is not required [45] for the development of allergen-induced AHR in mice. This suggests that epithelium and at least one other tissue type can contribute to the development of AHR. It was recently demonstrated that inhibition of arginase I in the lung prevented IL-13-induced AHR [61]. L-arginine is a substrate for eNOS in the generation of NO, a potent bronchodilator. It has been suggested that decreased production of NO due to substrate diversion of L-arginine to the arginase path-way might contribute to AHR in asthma [62]. Arginase I is expressed by smooth muscle and epithelial cells in the airways of subjects with asthma [63]. Although other cytokines might also contribute, IL-13 increases the expression of arginase I by GI epithelial cells [64], alveolar macrophages [65], airway fibroblasts [66] and vascular smooth muscle [67]. Therefore, AHR might occur as a consequence of the ability of IL-13 to induce arginase I in multiple cell types.

SUBEPITHELIAL FIBROSIS

The basement membrane (lamina reticularis) separates the airway epithelium from the mesenchyme. It is normally 3 to 4 μ m thick but the thickness of the basement membrane is increased two- to threefold in subjects with asthma [68,69]. IL-13 may contribute to the fibrotic thickening of basement membrane by directly activating fibroblasts to proliferate and produce collagen [70,71]. Alternatively, TGF- β has been strongly implicated in the development of fibrosis in asthma due to its potent proliferative and synthetic effects on fibroblasts and because its expression is increased in the airways of subjects with asthma [72]. Indeed, the profibrotic effect of IL-13 *in vivo* is proposed by Lee *et al.* to be mediated by TGF- β [73]. In their study, macrophages were identified as the major source of TGF- β 1 in the lung with lower contributions of TGF- β 1 being produced by airway and alveolar epithelial cells and eosinophils. In recent studies, Fichtner-Feigl *et al.* showed that IL-13 is critical for the induction of TGF- β by macrophages as well as the development of lung fibrosis induced by bleomycin treatment [74]. While the bleomycin model might not be entirely relevant to the mechanisms of fibrosis as it occurs in asthma, this study is worth noting in part because of the controversial IL-13-induced signaling pathway that was implicated. The first stage involves the induction of IL-13R α 2 on macrophages by the combined activity of TNF- α and either IL-4 or IL-13 and the second stage involves IL-13 signaling through the previously recognized decoy receptor, IL-13R α 2, which resulted in activation of the TGF- β 1 promoter *via* the transcription factor AP-1.

Alternatively, the eosinophil might be an important cell type that contributes to IL-13-induced airway fibrosis [75]. Eosinophils are important sources of TGF- β in asthma [76,77] and the treatment of asthmatics with an anti-IL-5 antibody resulted in decreased numbers of eosinophils in the airway associated with decreased TGF- β 1 levels in BAL fluid and reduced expression of matrix proteins in the bronchial mucosal [78]. However, other cellular

pathways might also contribute, as eosinophil deficient mice are only partially protected from IL-13-induced fibrosis [75].

IL-13 treatment of human airway epithelial cells in culture leads to the production of TGF- β . This effect of IL-13 has been proposed to contribute to subepithelial fibrosis by activation of the epithelial-mesenchymal tropic unit [79]. However, while constitutive transgenic IL-13 production in the lungs of STAT6 sufficient resulted in the development of subepithelial fibrosis [55] and significant increases in lung collagen content [44], the lung collagen content was not elevated by transgenic IL-13 production in the lungs of STAT6 deficient mice and only slightly elevated when IL-13-induced STAT6 signaling was limited to epithelial cells [44]. However, TGF- β family members are secreted in inactive latent complexes [80]. Therefore, IL-13 effects exclusively on epithelium might not have been sufficient for its extracellular activation.

EXCESSIVE MUCUS PRODUCTION

Goblet cells defined as mucin-filled, non-ciliated secretory cells in the surface epithelium are normally found in both upper and lower airways [81]. In asthma, excessive mucus is largely due to increased numbers of goblet cells and mucus gland hypertrophy [82]. Excessive mucus might contribute to luminal narrowing and increased airflow resistance. Also, excessive mucus might lead to early small airway closure in asthma by increasing the surface tension of the airway surface liquid [83,84]. Defining the mechanisms of excessive mucus production in asthma is important because mucus occlusion of airways have been strongly linked to deaths caused by asthma [85]. Generally, there is a consensus supporting a critical role for IL-13 in the development of goblet cell hyperplasia [86,87]. The *in vitro* evidence of an important role for IL-4R α signaling in epithelial cells is mixed with some reports showing that IL-13 or IL-4 treatment of cultured epithelial cells results in the induction of mucin genes [88,89] and other reports indicating that it does not [90,91]. *In vivo* studies of mice with STAT6 expression limited exclusively to epithelial cells [44] or IL-4R α expression excluded from these cells [45] indicate that IL-4 and/or IL-13 effects on epithelial cells is sufficient and necessary for the allergen-induced development of goblet cells in mice.

When raised under barrier conditions there are typically no goblet cells found in the airways of mice at baseline. However, within 24-48 hours following various treatments that induce allergic inflammation, goblet cells are easily identified in the surface epithelium. There is a debate as to the cellular identity of the goblet cell precursors. Some studies support the idea that goblet cells arise from non-ciliated secretory cells (Clara cells) that reside in the surface epithelium as IL-13 induces these cells to structurally reorganize and become loaded with mucin granules [45,92]. Other studies suggest that a combination of EGF receptor signaling and IL-13-induced STAT6 signaling in airway epithelial cells causes the transdifferentiation of ciliated epithelial cells to non-ciliated goblet cells [93]. Possibly both mechanisms contribute to goblet cell hyperplasia, although it remains to be determined to what extent one or the other pathway is predominant.

IL-4- AND IL-13-INDUCED MEDIATORS

A functionally diverse set of genes is expressed as a consequence of STAT6 signaling exclusively in epithelial cells of mice [43,44]. These include the gel-forming mucins, muc5ac and muc5b, and a STAT6-dependent product of goblet cells, termed calcium-activated chloride channel 3 (also referred to as gob-5) [94]. Inhibition of gob-5 prevented both mucus production and AHR [95,96] and gob-5 is expressed at higher than normal levels in the airway epithelium of subjects with asthma [43,97]. The amino acid sequence of gob-5 shows homology to a family of calcium-activated chloride channels [94]. That gob-5 might be an ion channel was supported by studies of nitluminic acid, a calcium-activated chloride channel blocker that inhibits goblet cell hyperplasia [98]. However, it was subsequently shown that gob-5 is not a membrane spanning protein [99] but is secreted by goblet cells [100] and therefore is unlikely to be an ion channel. It remains to be determined whether gob-5 is a signaling molecule and how niflumic acid inhibits mucus production.

Another IL-13-induced mediator of goblet cell hyperplasia has recently been identified, SAM pointed domain-containing ETS transcription factor (SPDEF) is induced in airway epithelial cells by IL-13, its induction is STAT6-dependent, and it directly interacts with the thyroid transcription factor 1 [101]. When transgenic SPDEF was expressed under control of an epithelial cell-specific promoter, it was sufficient to cause goblet cell hyperplasia in the airways of mice.

A more complete picture of how STAT6 signaling induces the development of goblet cells is emerging. Muc5ac is a major mucin product of goblet cells [102,103]. To our knowledge there are no reports of direct STAT6 regulation of promoters for mucin genes and there is not a consensus sequence motif present for STAT6 in the promoter regions of any mammalian Muc5ac ortholog [102]. Rather, HIF-1 α and SMAD4 binding sites have been identified as important regulators of Muc5ac promoter activity [102]. Therefore, it appears that IL-4 and/or IL-13 can initiate a cascade of STAT6-dependent signaling events in epithelial cells, probably involving gob-5 and SPDEF, that leads to the formation of goblet cells. However, it appears that STAT6 is not itself directly involved in mucin gene promoter regulation.

Another epithelial secreted factor termed trefoil factor 2 (Tff2) is induced by IL-13 effects exclusively on airway epithelial cells [44]. Its expression is increased in allergic mouse models of asthma [104] and increased in bronchial brushings retrieved from subjects with mild asthma [43]. However, Tff2 may be a protective molecule as it contributes to repair of injured GI epithelium [105] and genetic deletion of Tff2 does not alter the development of allergen-induced inflammatory responses in the lungs of mice [106].

Allergen sensitization and airways challenge as well as IL-13-induced STAT6 signaling exclusively in epithelial cells increases expression of 12/15-lipoxygenase (12/15-LO) in the lungs of mice [43]. 12/15-LO is a dioxygenase that converts arachidonic acid to 15-hydroperoxyeicosatetraenoic acid (15-HPETE) and 12-HPETE. Its human ortholog, 15-L0-1, is induced by IL-4 treatment of cultured airway epithelial cells [107]. The expression of 15-L0-1 is dramatically increased in airway epithelium and inflammatory cells within the

airways of subjects with severe asthma [108] and somewhat induced in bronchial brushings retrieved from the airways of asymptomatic asthmatics [43]. However, its biologic function in the airway has remained elusive. Our recent studies point to 12/15-LO as a potent inhibitor of mucosal specific IgA production in the lungs of mice [109]. This may be important as decreased levels of IgA in serum and decreased secretory IgA in BAL fluid correlate with worsening asthma severity [110].

In a recent clinical study, increased gene expression of a novel carbohydrate-binding calcium-dependent lectin, termed intelectin (Itln), was detected in bronchial brushings from subjects with mild asthma [43]. Its expression is induced by IL-13 treatment of cultured normal human bronchial epithelial cells [43]. Itln is identical to the lactoferrin receptor, it is a member of the transferrin family of iron-binding proteins and it binds to galactofuranose, a sugar present on the cell surface of many microorganisms [111]. The importance of protein-carbohydrate interactions is increasingly being recognized [112]. Presumably Itln can protect the host by binding to microorganisms directly or by sequestering iron from the microenvironment. However, immunohistochemical studies of Itln indicate that it is secreted by goblet cells and paneth cells and it localizes to the brush border of GI epithelium. It has been suggested that this pattern might reflect Itln binding to glycolipids with terminal galactose residues at the epit-helial surface and therefore Itln might protect the host by blocking sites used by bacteria to adhere to cells [113]. However, transgenic Itln overexpression by epithelial cells did not alter immune responses to or the ability of mice to clear lung infections caused by the parasitic worm *Nippostrongylus brasiliensis* or *Mycobacterium tuberculosis* [114]. The function of Itln has yet to be defined. Nonetheless, Itln is an epithelial-expressed and STAT6-dependent gene worthy of further study.

Recently, expression of a molecule termed acidic mammalian chitinase (AMCase) was shown to be induced by IL-13 in airway epithelial cells and macrophages in the lungs of mice and increased expression of AM-Case in airway epithelial cells and macrophages was associated with asthma [115]. AMCase degrades chitin, one of the most abundant biomolecules on earth, a compound present in fungi, crustaceans, helminths and insects. Exposure of mice to chitin in the airways resulted in macrophage activation and recruitment of eosinophils and basophils but the chitin-induced inflammation was largely prevented when transgenic AMCase was constitutively expressed in the lung [116]. In this case, with chitin present in the lung, AMCase had a protective role. In contrast, antibody or chemical inhibition of AMCase resulted in a moderate decrease in IL-13-induced chemokine expression and inflammation [115], indicating that AMCase itself might contribute to allergic inflammation when chitin is not present.

CONCLUSIONS

In summary, IL-4 and/or IL-13 mediated airway epithelial cell responses likely contribute to gob-5- and SPDEF-dependent excessive mucus production. IL-4 and/or IL-13 mediated airway smooth muscle cell and epithelial cell responses may contribute to the development of AHR, and either pathway might involve induction of arginase I. IL-4 and/or IL-13 induce airway epithelial expression of chemokines *in vitro*. However, an important role for IL-4 and/or IL-13 induced epithelial chemokine production and recruitment of inflammatory cells

into the airway has not been confirmed *in vivo*. Alternatively, IL-4 and/or IL-13 effects on dendritic cells may contribute to allergic inflammation. IL-4 and/or IL-13 effects on macrophages and eosinophils might contribute to the development of subepithelial fibrosis by inducing production of TGF- β . We propose a working model of the pathologic cellular events mediated by IL-4 and IL-13 in the allergic airway (Illustration 2).

Inhibition of STAT6 as a potential asthma therapy may be difficult since it is an intracellular target. Blockade of IL-4R α would be predicted to provide benefit by blocking the effects of both IL-4 and IL-13. However, the inhibition of IL-4-mediated signaling in T-helper cells might have the disadvantage of preventing Th2 differentiation and consequently impairing anti-parasite immunity. Further, blockade of IL-4 alone in the airways might not be an effective treatment due to the persistence of IL-13. However, blockade of IL-13 alone in the airways has proven to be an effective treatment in pre-clinical models of asthma in mice [52,54], in sheep [117], and in non-human allergic primates [118]. It remains to be determined whether targeting IL-13 in the airway will improve the condition of patients with asthma.

ABBREVIATIONS

IL	Interleukin
STAT6	signal transducer and activator of transcription factor 6
IRS	insulin receptor substrate
JAK	janus kinase
14R	insulin/IL-4 receptor motif
PI3-K	phosphoinositol 3-kinase
ITIM	immunoreceptor tyrosine-based inhibitory
motif SHP-1	SH2-containing tyrosine phosphatase-1
SHIP	SH2-containing inositol 5'-phosphatase
AHR	airway hyperresponsiveness
ASM	airway smooth muscle
NO	nitric oxide
gob-5	calcium-activated chloride channel 3
SPDEF	SAM pointed domain-containing ETS transcription factor
Tff2	trefoil factor 2
12/15-LO	12/15-lipoxygenase
HPETE	hydroperoxyeicosatetraenoic acid
Itln	intelectin
AMCase	acidic mammalian chitinase

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Fig. (1). Illustration 1. IL-4 and IL-13 signaling pathways

IL-4 is a ligand of the type III IL-4 receptor composed of common γ and IL-4R α subunits. Both IL-4 and IL-13 are ligands of the type II IL-4 receptor composed of IL-4R α and IL-13R α 1 subunits. Receptor heterodimerization leads to activation of janus kinase (JAK) family members which phosphorylate tyrosine residues in the cytoplasmic tail of IL-4R α . This leads to homodimerization of signal transducer and activator of transcription factor 6 (STAT6) monomers which then translocate to the nucleus and bind to the promoter regions of various genes. In concert, phosphorylated insulin receptor substrate (IRS) molecules provide binding sites for several src-homology domain 2 containing enzymes and adapter proteins. The downstream IRS-mediated signaling cascades include those mediated by phosphoinositol 3-kinase (PI3-K). The type I IL-4 receptor is shown in the activated, ligand-bound form and the type II IL-4 receptor is shown at rest.

Fig. (2). Illustration 2. A working model of the cellular mechanisms by which IL-4- and IL-13 induce pathology in the airways

IL-4/13 effects on dendritic cells contribute to inflammation. IL-4/13 effects on airway smooth muscle and epithelium contribute to airway hyperreactivity (AHR). IL-4/13-induced transforming growth factor beta (TGF- β) production by macrophages and eosinophils contributes to subepithelial fibrosis. IL-4/13 effects on airway epithelial cells contribute to excessive mucus production.