

IL-13/IL-13 Receptor Interaction, an Emerging Therapeutic Target in Allergic Disease

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ABSTRACT

Interleukin (IL)-13 is a Th-2 cytokine, known to be involved in allergic diseases. Although IL-13 and another Th-2 cytokine, IL-4, share receptors and signal pathways, having similar biological properties, the critical role of IL-13 alone *in vivo* in the pathogenesis of bronchial asthma has recently been recognized, based mainly on analyses of mouse models. IL-13 and its signal pathway are thought to be promising targets to develop a therapeutic agent for bronchial asthma. In this article, we summarize the signal transduction pathway of IL-13, the pathological roles of IL-13 in bronchial asthma, and possible therapeutic strategies to block the IL-13 signal.

KEY WORDS

allergy, antagonist, asthma, drug design, interleukin-13, receptor

INTRODUCTION

Bronchial asthma is a complex disease caused by a combination of multiple genetic and environmental factors.^{1,2} Improved hygiene, resulting in a decrease in childhood infections, has been thought to be an important environmental factor.^{3,4} This would explain why the prevalence of allergic diseases, including bronchial asthma, has dramatically increased in developed areas in the last few decades. By contrast, genetic factors must have been unchanged in such a relatively short period. Although hundreds of researchers have listed several potential genetic factors that may affect disease susceptibility, there has been no successful attempt to target any specific genetic factors to treat bronchial asthma.^{5,6} Nevertheless, a growing body of genetic and clinical evidence that these cytokines are critical in the pathophysiology of asthma both in mouse and human, raises the possibility that inhibition of T helper (Th)-2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 could be a logical approach to asthma therapy.^{6,7} Of these, we summarize here the pathophysiological roles of IL-13 in bronchial asthma and the therapeutic strategies to inhibit its signaling pathway.

IL-13 RECEPTOR SYSTEM

IL-13 is a pleiotropic cytokine, playing key roles in the pathogenesis of allergic diseases such as bronchial asthma and atopic dermatitis, and in the host defense processes against parasite infection.⁷⁻⁹ It exerts its many actions through interaction with specific receptors expressed on the surface of target cells (Fig. 1). IL-13 binds to a low-affinity IL-13 receptor $\alpha 1$ chain (IL-13R $\alpha 1$)^{10,11} or to a high-affinity IL-13 receptor $\alpha 2$ chain (IL-13R $\alpha 2$).^{12,13} IL-13/IL-13R $\alpha 1$ complex recruits the second receptor subunit, IL-4 receptor α chain (IL-4R α), which is also the high-affinity α -receptor subunit for IL-4. This oligomerization activates the Janus kinases (JAKs) to phosphorylate tyrosine residues of the signaling molecules, including the signal transducer and activator of transcription (STAT) proteins. Phosphorylated STAT-6 in turn migrates to the nucleus and activates transcription of genes encoding germline ϵ transcript, CD 23, and MHC class II in B cells, IL-4 and IL-13 in T cells, CCL 11 (eotaxin) in fibroblasts, and a chloride channel human CLCA1 (mouse CLCA3) in bronchial epithelial cells.⁸ As either IL-13 or IL-4 activates STAT-6 through a shared receptor chain, IL-4R α , they share most biological activities.^{7,14-16} IL-13R $\alpha 2$ binds IL-13

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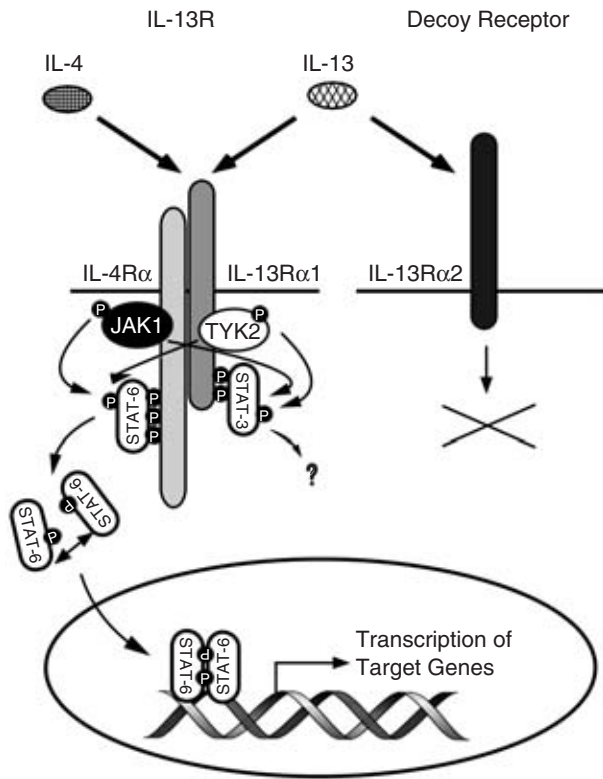


Fig. 1 The receptor structure and signal transduction mechanism of IL-13. IL-13 binds to IL-13 receptor (IL-13R), which is composed of IL-4R α and IL-13R α 1. IL-13R also acts as IL-4R. Engagement of the receptor causes signal transduction, mainly through the JAK-STAT pathway. IL-13 also binds to IL-13R α 2, although this receptor does not transduce the signal, acting as a decoy receptor.

with even higher affinity than IL-13R α 1 but appears to be a non-signaling “decoy” receptor, because it is not known to oligomerize with any cytokine receptor subunit upon binding of IL-13 and its cytoplasmic tail is too short to transduce intracellular signals.^{13,17} When IL-13R α 2 is expressed on some cell lines, STAT-6 activation by IL-13 via IL-13R α 1-containing receptor complex is blocked, because IL-13 is competitively bound by IL-13R α 2.¹⁷⁻¹⁹

The biological activities of IL-4 and IL-13 are very similar because of their shared receptor system. However, knocking out the *IL13* gene but not the *IL4* gene in mice prevents the development of asthmatic phenotypes upon allergen challenge.²⁰ Thus, the *in vivo* function of IL-13 seems to be different from that of IL-4, which can signal without IL-13R α 1 in most immune cells with the help of the IL-2 receptor γ chain. In T cells, which lack IL-13R α 1, IL-13 transduces very little amount of signal; in resting B cells, which express the receptor at a very low level, IL-13 is similarly weak.^{14,21} In contrast, IL-13R α 1 is abundantly expressed in many non-hematopoietic tissues, including

lung.^{22,23} Although it is uncertain whether an IL-13-specific signal is present in such tissues, the predominant activity of IL-13 may be deduced by the different spatial and temporal patterns of expression of IL-4, IL-13, and their receptor subunits in the tissue. Consequently, the biological activities of IL-4 and IL-13 *in vivo* are skewed towards immune cells and non-immune tissues, respectively.⁷

SIGNIFICANCE OF IL-13 IN THE PATHOGENESIS OF BRONCHIAL ASTHMA

Bronchial asthma is caused by various genetic and environmental factors,¹ which result in infiltration of Th-2 lymphocytes, mast cells, and eosinophils into the bronchial lesions with downstream inflammatory mediators released, impairing the airway function.^{7,8} Cytokines derived from the Th-2 lymphocytes are considered to orchestrate the asthmatic phenotype. Among the Th-2 cytokines, substantial evidence supports key roles for IL-4 and IL-13 in the pathogenesis of bronchial asthma. Such evidence is classified into the following categories.

ANALYSES OF MOUSE MODELS

Analyses of knock-out mice for any components of the IL-4 and IL-13 signal transduction system including IL-4, IL-13, IL-4R α and STAT-6 have revealed that both cytokines play a pivotal role in induction of airway hyperresponsiveness (AHR). Furthermore, either epithelial overexpression of an *IL13* transgene or administration of IL-13 to mice has shown that IL-13 alone can induce many of the features of asthma, including AHR, mucus hypersecretion, and airway fibrosis.²⁴⁻²⁶ It has been further revealed that the target cells of IL-13 in such situations are mainly bronchial epithelial cells.²⁷

EXPRESSION OF IL-4 AND IL-13 IN THE BRONCHIAL LESIONS

Augmented expression of IL-4 and IL-13 in bronchial tissues or bronchoalveolar lavage fluids derived from asthma patients is observed at the baseline and after allergen challenge. Particularly, IL-13 is predominantly expressed, compared to IL-4.^{28,29}

GENETIC ASSOCIATION OF THE IL-4 AND IL-13 SIGNALING MOLECULES

Genetic predisposition to allergic diseases is thought to be polygenic, and the genetic factors are thought to exist among genetic polymorphisms.³⁰ Extensive efforts have been made to identify such factors by genome-wide scanning and by candidate-gene studies. Based on the latter, it has been reported that several genetic polymorphisms of genes encoding IL-4 and IL-13 signaling molecules such as *IL4*, *IL13*, *IL2RG*, *IL4RA*, *IL13RA1*, *STAT6*, and *BCL6* are genetically associated with asthma or atopic status.³¹ Among the single nucleotide polymorphisms (SNPs)

that are demonstrated to be associated with bronchial asthma or atopy, we have analyzed the functional properties of variants of *IL4RA* (Ile50Val) and *IL13* (Gln110Arg). The variant of IL-4R α whose amino acid at 50 is isoleucine upregulates response to IL-4, leading to increased activation of STAT-6 and IgE synthesis, compared to the valine type.^{32,33} The variant of IL-13 whose amino acid at 110 is glutamine has less affinity with IL-13R α 2, a decoy receptor, and an enhanced stability, compared to the arginine type, causing upregulation of the IL-13 concentration *in vivo*.^{22,34} These results clearly show that genetic variation is not only a disease-susceptibility marker but also a causative factor for a biologically functional difference.

TARGETING IL-13 TO DEVELOP A NEW AGENT FOR ALLERGIC DISEASES

In general, there are several possible approaches to targeting specific cytokines. These include drugs that inhibit cytokine production such as glucocorticoids and tacrolimus, blocking antibodies to cytokines or their receptors; soluble receptors to adsorb secreted cytokines; and low molecular weight compounds that potentially block the signal transduction pathways activated by cytokine receptors.

Because Th-2 cytokines have a critical role in the pathogenesis of allergic diseases, particularly of bronchial asthma, it is reasonable that blocking their biological activities should be an ideal strategy to treat bronchial asthma.^{6,7,35} The potential target is either IL-4 or IL-5 or IL-13. However, anti-IL-4 and anti-IL-5 therapies have been withdrawn because of their insignificant effect for treating AHR.^{35,36} Clinical trials of humanized anti-IL-5 antibody to asthma showed that this antibody was not effective for AHR, although it was effective for reduction of eosinophilia in blood and, to a lesser extent, in lung tissues, inhibiting airway remodeling.^{36,37} A single nebulized dose of soluble IL-4R α (sIL-4R α) prevents the decrease in lung function induced by withdrawal of inhaled corticosteroids in patients with moderately severe asthma,³⁸ and weekly nebulization of sIL-4R α improved asthma control over a 12-week period.³⁹ However, subsequent studies in patients with milder asthma proved that it was not significantly effective.³⁵

These facts, together with a substantial body of evidence that IL-13 is a central mediator in the pathogenesis of bronchial asthma, prompted us to explore whether the blockage of IL-13 could work for diminishing the asthmatic phenotypes, including AHR. Because we focused on the IL-13/IL-13 receptor interaction as a therapeutic target in this article, potential IL-13 inhibitors at the receptor level are listed below (Table 1).

SOLUBLE IL-13R

Blocking actions of cytokines by administration of

their soluble receptors is now widely accepted as a promising strategy for treating various diseases. For example, soluble TNF receptor (Enbrel[®]) has been shown to be effective for rheumatoid arthritis.⁴⁰ As mentioned earlier, it has been shown that IL-13 is more important than IL-4 in inducing asthmatic phenotypes in the mouse, and that sIL-4R α that blocks IL-4 but not IL-13 was so ineffective that further development of sIL-4R α as a potential therapeutic modality was terminated. Based on such results, a recombinant soluble IL-13R (sIL-13R) has also been considered for asthma treatment. Two candidates of sIL-13R exist: sIL-13R α 1 and sIL-13R α 2. Because the affinity of IL-13R α 2 with IL-13 (K_d; 50–500 pM) is more than 10-fold higher than that of IL-13R α 1 (K_d; 4 nM), sIL-13R α 2 has superior potency as a blocking agent.^{10,11,34} In a mouse model, an inhaled administration of sIL-13R α 2-Fc protein was reported to be effective for suppressing AHR and eosinophilia.^{25,26} For human asthma, a recombinant protein denoted IL-4/13 Trap, in which sIL-13R α 1 and sIL-4R α are tandem lined,⁴¹ was developed, and is being evaluated in Phase I clinical testing. Further trials conducted with asthma patients are awaited.

IL-4 MUTEIN

Some bioengineered versions (muteins) of IL-4 have been developed. These include variants whose tyrosine at 124 is replaced with aspartate (Y124D), and arginine at 121 is additionally replaced with aspartate (R121D/Y124D). The R121D/Y124D mutein acts as an IL-4/IL-13 antagonist because it is able to bind to the shared receptor subunit, IL-4R α , but not able to transduce the signal.^{42,43} Multi-center Phase I clinical safety trials of this molecule to asthma have already started. A recent study with a mouse model has shown that, although a mouse version of IL-4 mutein can efficiently prevent the development of the asthmatic phenotype when applied during allergen challenge, it is ineffective when applied after allergen challenge.⁴⁴ Because an IL-13-specific inhibitor, sIL-13R α 2-Fc, can prevent asthma development in mice when applied even after allergen challenge,²⁵ this means that IL-13 could act without IL-4R α to modulate pathogenesis.⁴⁵

OTHER IL-13 ANTAGONISTS

In mouse models, immunoneutralization of IL-13 but not IL-4 has been shown to be effective in fungus-induced asthma and in respiratory syncytial virus-induced AHR.^{46,47} However, anti-IL-13 antibody has never been applied to human asthma treatment.

A STRATEGY FOR APPLYING THE FINDINGS ABOUT THE IL-13 VARIANT TO THE DEVELOPMENT OF A NEW AGENT

As described earlier, the affinity of IL-13 with IL-13R α 2 is much higher than IL-13R α 1. Analyses of

Table 1 List of IL-13 Antagonist

Agent	IL-4 block	IL-13 block	References
Soluble IL-13R α 2-Fc	—	+	25, 26
IL-4/13 Trap (IL-13R α 1/IL-4R α chimera)	+	+	41
IL-4 mutein (R121D/Y124D)	+	+	42, 43, 44
Anti-IL-13R α 1 Antibody	?	+	46, 47

the IL-13 variant have demonstrated that the variant which bears glutamine at amino acid 110 (Gln110) has a lower affinity with IL-13R α 2 than the arginine type (Arg110), whereas both IL-13 proteins show the same affinity with IL-13R. ³⁴ To explain these binding properties with respect to molecular structure, we have constructed a homology model of the complex (Arima K., unpublished data). According to this model, it is initially predicted that there exist five ionic interactions between amino acid residues of IL-13 and IL-13R α 2. In contrast, only three ionic interactions are predicted between IL-13 and IL-13R α 1. The loss of two ionic interactions could explain why the affinity of IL-13 with IL-13R α 1 is lower than IL-13R α 2. In this context, the IL-13 variant (Gln110) is assumed to lose one ionic bond compared with Arg110, weakening the affinity with IL-13R α 2, whereas it does not affect the affinity with IL-13R α 1.

We are now attempting to validate this model by incorporating mutations into the ligand/receptor interface, including predicted ionic interaction residues. We have found that some interactions other than ionic bonds are involved in determining the affinity of IL-13/IL-13R interaction (Arima K., unpublished data). If a finely tuned structural model is reconstructed based on the data from mutagenesis experiments, we may be able to manipulate the affinity between IL-13 and the IL-13 receptor by incorporating additional interactive side chains or depleting unfavorable ones. If we could find a mutated type of IL-13R α 2 that binds IL-13 more firmly, we would be able to use such a "super receptor" to produce a remodeled sIL-13R α 2 that would trap IL-13 more efficiently. Thus there is a possibility that functional findings based on the genetic polymorphisms associated with some diseases might be of great use not only as disease-susceptibility markers but also for developing new therapeutic approaches.⁴⁸

CONCLUSION

In this review article, we described the mechanism of signal transduction of IL-13, the significance of IL-13 in pathogenesis of bronchial asthma, and the possible development of novel therapeutic methods for allergic diseases by targeting the IL-13 signal. It is expected that in the near future, several drugs will emerge based on these strategies, giving us a wider choice of treatments, depending on the pathogenesis of the diseases.

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