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IL-13 receptors and signaling pathways: An evolving web

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IL-13 is an immunoregulatory cytokine secreted predominantly by activated T_H2 cells. Over the past several years, it has become evident that IL-13 is a key mediator in the pathogenesis of allergic inflammation. IL-13 shares many functional properties with IL-4, stemming from the fact that they share a common receptor subunit, the α subunit of the IL-4 receptor (IL-4R α). Characterization of IL-13-deficient mice, IL-4-deficient mice, and IL-4 receptor α -deficient (IL-4R $\alpha^{-/-}$) mice have demonstrated nonredundant roles for IL-13. IL-13 mediates its effects by interacting with a complex receptor system comprised of IL-4R α and two IL-13 binding proteins, IL-13R α 1 and IL-13R α 2. IL-13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells. However, functional IL-13 receptors have not been demonstrated on human or mouse T cells. Thus unlike IL-4, IL-13 does not appear to be important in the initial differentiation of CD4 T cells into T_H2-type cells but rather appears to be important in the effector phase of allergic inflammation. This is further supported by many *in vivo* observations, including that administration of IL-13 resulted in allergic inflammation, tissue-specific overexpression of IL-13 in the lungs of transgenic mice resulted in airway inflammation and mucus hypersecretion, IL-13 blockade abolished allergic inflammation independently of IL-4, and IL-13 appears to be more important than IL-4 in mucus hypersecretion. Given the importance of IL-13 as an effector molecule, regulation at the level of its receptors might be an important mechanism of modulating IL-13 responses and thus propagation of the allergic response. Accordingly, IL-13 is an attractive, novel therapeutic target for pharmacologic intervention in allergic disorders. This review will summarize the current understanding of the IL-13 receptors and signaling pathways, emphasizing recent observations. (*J Allergy Clin Immunol* 2003;111:677-90.)

Key words: IL-13, cytokine, receptor, Janus kinase, signal transducer and activator of transcription, suppressor of cytokine sig-

naling, protein inhibitor of activated signal transducer and activator of transcription, review

IL-13 is a critical mediator of allergic inflammation. Although it shares many functional properties with IL-4, it has been shown to have distinct functions. Furthermore, IL-13 is more important than IL-4 in the development of airway hyperreactivity and mucus production. As such, it is an obvious target for pharmacologic intervention in the treatment of asthma. It is imperative to have a solid basic understanding of IL-13 functions, receptors, and signaling pathways to design and generate effective drugs to target the IL-13 response. Considerable research effort is taking place to understand this important cytokine, how it transmits its effects, and the mechanisms by which its signaling and responses are regulated. The purpose of this article is to provide a comprehensive review of the current understanding of IL-13 receptors and signaling pathways. First, the functions of IL-13 will be reviewed. Its receptors are widely expressed, and consequently, IL-13 has many diverse effects on different cell types. Next, the components of the IL-13 receptor complex and the signaling pathways that are activated after receptor engagement will be detailed. The mechanisms by which IL-13 signaling is regulated will be discussed. Atopy-associated genetic variants of IL-13 and its receptor subunits have been described, and these data will be reviewed.

IL-13

Characterization and structure

IL-13 was first described in 1989 as P600, a protein preferentially produced by activated mouse T_H2 cells.¹ The cDNA for human IL-13 was cloned approximately 10 years ago by 3 groups.²⁻⁴ It has a single open-reading frame with 132 amino acids, including a 20-amino-acid signal sequence that is cleaved from the mature secreted protein. Transfection of the cDNA into COS-7 cells has demonstrated that IL-13 is secreted as a 10-kd unglycosylated species.⁵ IL-13 belongs to the class of type I cytokines and shares the tertiary structure defined by a 4 α -helical hydrophobic bundle core.⁶ Although IL-13 only shares 25% homology with IL-4 at the amino acid level, the 25-amino-acid hydrophobic structural core is completely conserved, with only some conservative

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Abbreviations used

CIS:	Cytokine-inducible SH2-containing protein
γ c:	Common γ chain
IRS:	Insulin receptor substrate
ITIM:	Immunotyrosine-based inhibitory motif
JAK:	Janus kinase
NES:	Nuclear export signal
PI3:	Phosphoinositol 3
PIAS:	Protein inhibitor of activated signal transducer and activator of transcription
SHP-1:	SH2 domain-containing tyrosine phosphatase 1
SOCS:	Suppressor of cytokine signaling
STAT:	Signal transducer and activator of transcription

hydrophobic substitutions.⁷ IL-4 structure has been defined by means of crystallography and nuclear magnetic resonance studies^{8,9}; however, the tertiary structure of IL-13 is not known. Mass spectrophotometric studies have revealed that in contrast to IL-4, IL-13 contains only 2 disulfide bridges instead of 3.¹⁰ The crystallization of IL-13 and its receptors will provide very valuable information about the structure and, consequently, important clues about the function of these key molecules.

As outlined above, IL-4 and IL-13 share many structural characteristics; however, they also have some important differences. One notable difference between the 2 cytokines is in their abilities to act across species. IL-4 is absolutely species specific, such that human IL-4 acts only on human cells, and mouse IL-4 acts only on mouse cells.¹¹ In contrast, IL-13 is not species specific. Mouse IL-13 acts on human or mouse cells with equal potency. However, IL-13 does appear to be species selective because human IL-13 has greater activity on human cells than on mouse cells.^{2,5}

The gene encoding IL-13 is comprised of 4 exons and 3 introns and is located 12 kb upstream of the gene encoding IL-4 on chromosome 5q31, and both genes are in the same orientation.¹² This chromosomal region, 5q31, also contains the genes encoding IL-3, IL-5, IL-9, and GM-CSF^{4,12} and has been linked with asthma.¹³⁻¹⁶

IL-13 functions

IL-13 has many diverse functions on a wide variety of cell types that are relevant to the pathogenesis of allergic disorders, as shown schematically in Fig 1. These activities highlight the potent immunoregulatory role of IL-13. In human B cells human IL-13 has similar effects as IL-4, including promoting B-cell proliferation and inducing class switching to IgG4 and IgE in combination with CD40/CD40 ligand costimulation¹⁷ and inducing expression of surface antigens, including the low-affinity IgE receptor CD23 (Fc ϵ RII) and MHC class II.⁷ In monocytes and macrophages IL-13 enhances the expression of many members of the integrin family important in adhesion, including CD11b, CD11c, CD18, and CD29,¹⁸ and induces MHC class II and CD23 expression.¹⁹ In addition, IL-13 inhibits the production of pro-inflammatory mediators by monocytes and macrophages, including prostaglandins,²⁰ reactive oxygen and nitrogen interme-

diates,^{21,22} IL-1, IL-6, IL-8, TNF- α , and IL-12,¹⁹ through a mechanism that partially involves suppression of nuclear factor κ B.²³ IL-13 has been reported to have direct effects on eosinophils, including promoting eosinophil survival, activation, and recruitment.²⁴⁻²⁶ IL-13 has been reported to activate mast cells and contributes to IgE priming of mast cells given its role in promoting IgE synthesis.¹⁹

IL-13 also has important functions on nonhematopoietic cells, including endothelial cells, smooth muscle cells, fibroblasts, and epithelial cells. In endothelial cells IL-13 is a potent inducer of vascular cell adhesion molecule 1, which is important in the recruitment of eosinophils.²⁷ IL-13 enhances proliferation and cholinergic-induced contractions of smooth muscle cells in vitro²⁸ and induces type I collagen synthesis in human dermal fibroblasts.²⁹ In epithelial cells IL-13 is a potent inducer of chemokine expression,³⁰ alters mucociliary differentiation,³¹ decreases ciliary beat frequency of ciliated epithelial cells,³¹ and results in goblet cell metaplasia.³²⁻³⁴

The net effect of these functions is to promote inflammation associated with allergic disorders and to promote changes in the airway epithelium that contribute to the pathology of asthma, while contributing to the control of helminthic infections and suppressing inflammation associated with bacterial and most viral infections. Notably, IL-13 has been reported to have no effects on mouse B cells or human or mouse T cells.¹⁸ Thus unlike IL-4, IL-13 does not appear to be important in the initial differentiation of CD4 T cells into T_H2-type cells but rather appears to be important in the effector phase of allergic inflammation. This effector role, which has been further supported by many observations in vivo, including administration of IL-13, resulted in allergic inflammation,^{32,34} tissue-specific overexpression of IL-13 in the lungs of transgenic mice resulted in airway inflammation and mucus hypersecretion,³³ IL-13 blockade abolished allergic inflammation independently of IL-4,^{32,34} and IL-13 appears to be more important than IL-4 in mucus hypersecretion.³⁵ The effects of IL-13 on airway hyperreactivity and mucus production are independent of IL-5 and the chemokine eotaxin.³⁶ Further evidence that IL-13 is a critical effector molecule was recently provided by a study in which IL-13 was inducibly expressed in the lungs of mice.³⁷ Interestingly, IL-13 was found to be a potent stimulator of matrix metalloproteinases and cathepsin proteases in the lung, and overexpression of IL-13 in the adult lung (by feeding doxycycline to the mice) resulted in emphysematous changes and mucus metaplasia.³⁷ Thus IL-13 is an important effector molecule both in asthma and in chronic obstructive pulmonary disease phenotypes.

There is considerable evidence that IL-13 has some unique functions in vivo independent of IL-4. Some of these are discussed above, and additional evidence has been compiled by comparing IL-4^{-/-}, IL-13^{-/-}, STAT6^{-/-}, and IL-4R α ^{-/-} mice in models of allergic inflammation²⁸ and helminth infection.³⁸ The IL-4^{-/-} and IL-13^{-/-} mice are deficient in IL-4 and IL-13, respectively, whereas the

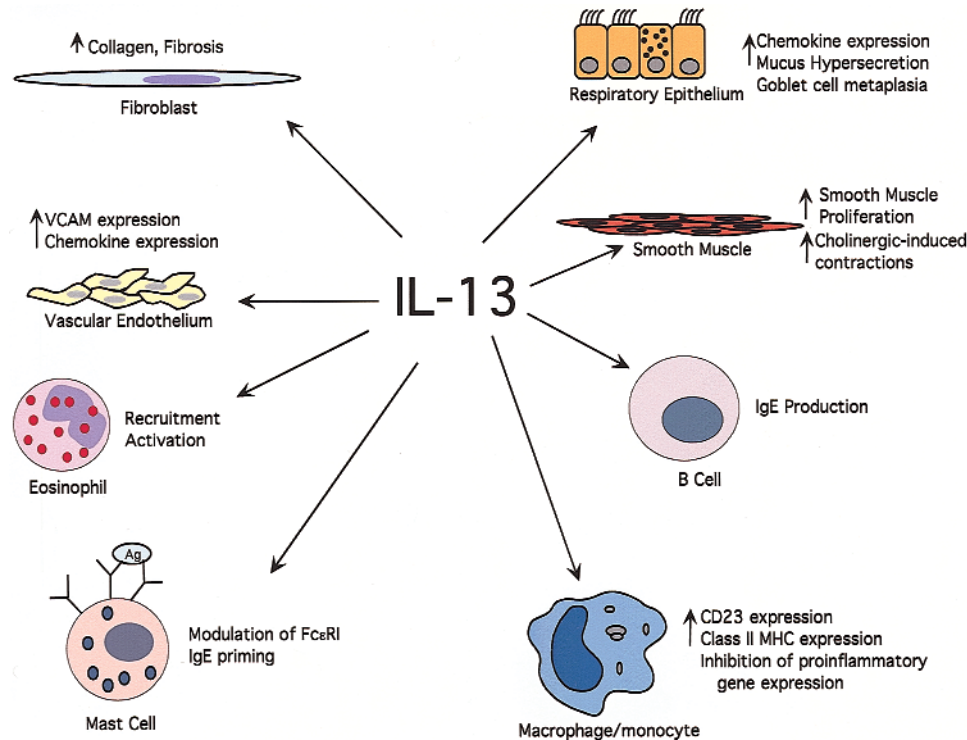


FIG 1. Overview of actions of IL-13 on hematopoietic and nonhematopoietic cells.

STAT6^{-/-} and IL-4Rα^{-/-} mice are deficient in both IL-4- and IL-13-mediated responses because STAT6 and IL-4Rα are shared components of both the IL-4 and IL-13 receptor signaling pathways. Thus differences noted between the IL-4^{-/-} and IL-4Rα^{-/-} mice are attributed to IL-13. For example, IL-4^{-/-} mice display normal expulsion of *Nippostrongyloides brasiliensis*, but the IL-4Rα^{-/-} mice, and the STAT6^{-/-} mice are unable to expel *N brasiliensis*, suggesting that IL-13, which is the only other known cytokine that uses IL-4Rα and STAT6, is responsible for IL-4-independent protection. Differences between IL-4 and IL-13 responses might be due to differences in their receptors and signaling pathways.

IL-13 AND IL-4 RECEPTORS

IL-13 is a type I cytokine, and it signals through type I cytokine receptors. Type I cytokine receptors are defined by several features, including 4 conserved cysteine residues, a W-S-X-W-S motif, fibronectin type II modules in the extracellular domain, and proline-rich box regions in the intracellular domain that are important for binding of Janus tyrosine kinases (JAK).⁶ These receptors have no intrinsic kinase activity but rather have constitutively associated JAKs, which ultimately result in recruitment of downstream signaling molecules. Type I cytokine receptors form heterodimers. There are a total of 4 receptors between IL-4 and IL-13, and these are shown schematically in Fig 2.

IL-4Rα

Both IL-4 and IL-13 use the IL-4Rα chain as a component of their receptors. IL-4Rα is a 140-kd protein that binds IL-4 with high affinity (dissociation constant = 100 pmol/L). Its cDNA encodes an open reading frame of 825 amino acids, including a 25-amino-acid signal sequence.^{39,40} IL-4Rα has the characteristic features of a type I cytokine receptor with 4 conserved cysteines and the W-S-X-W-S motif in the extracellular domain. It contains a single transmembrane domain and a long intracellular domain, which contains a membrane proximal Box-1 sequence that serves as a docking site for JAK1 and 5 conserved tyrosine (Y) residues at positions Y497, Y575, Y603, Y631, and Y713. IL-4Rα is constitutively expressed in relatively low numbers (a few hundred to a few thousand) on every cell type that has been tested¹¹ and is a component of both the type I and type II IL-4 receptors. The type I IL-4 receptors result from association of IL-4Rα with the common γ chain (γc), which is also a component of the receptors for IL-2, IL-7, IL-9, and IL-15.⁶ The γc does not bind IL-4 or IL-13 but is important for signaling of the type I receptor. Evidence that IL-4Rα is also a component of the IL-13 receptor comes from studies using potent IL-4Rα antagonists. These antagonists blocked IL-4Rα and were found to inhibit both IL-4 and IL-13 responses.^{41,42} Further support was provided by studies that demonstrated that both IL-4 and IL-13 responses were inhibited by blocking antibodies against IL-4Rα.^{43,44}

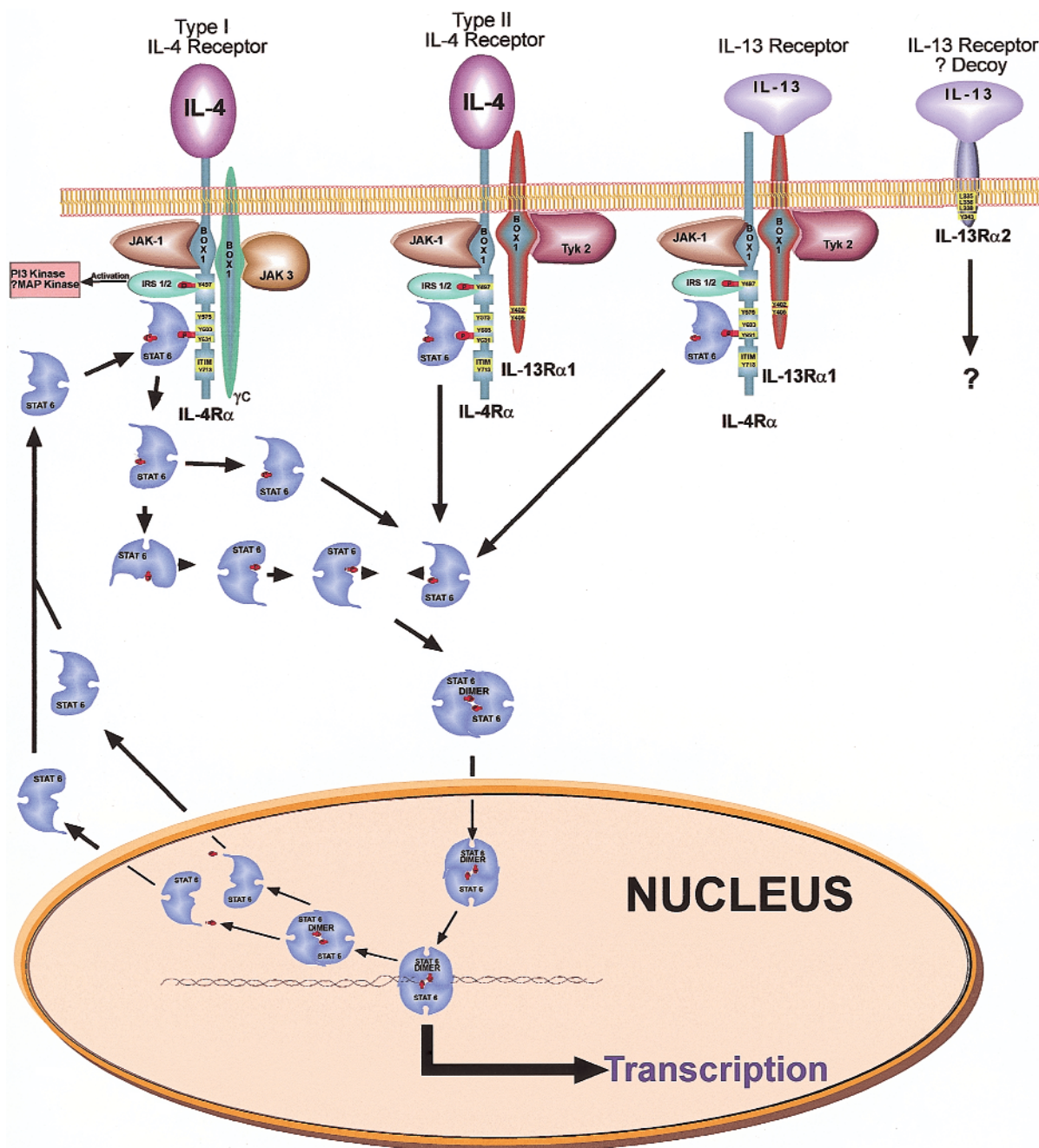


FIG 2. Schematic representation of IL-4 and IL-13 receptors and signaling pathways. The type II IL-4 receptor is also the functional receptor for IL-13 and is comprised of IL-4R α and IL-13R α 1. Signaling is mediated predominantly through IL-4R α and results in activation of the JAK/STAT and IRS-1/IRS-2 pathways. IL-13R α 2 binds IL-13 with high affinity but does not signal and has been hypothesized to act as a decoy receptor. [A larger version of this illustration is available in the online Journal at (www.mosby.com/jaci).]

Type II IL-4R/IL-13R

The central role played by the γ c in the signaling of multiple cytokines is the basis for the profound immunodeficiency observed in human patients when the γ c is mutated.⁴⁵ Cells derived from these patients were a useful tool to study the role of the γ c in signaling and demonstrated that both IL-

4 and IL-13 responses were intact, even in the absence of the γ c.⁴⁶ This suggested the presence of an alternate receptor for IL-4 and IL-13. It is now known that this alternate receptor is a heterodimer, the type II IL-4 receptor or the IL-13 receptor, which is comprised of IL-4R α and IL-13R α 1.

IL-13 has 2 cognate receptors, IL-13R α 1 and IL-13R α 2.⁴⁷⁻⁵² Both IL-13R α 1 and IL-13R α 2 are members of

the hematopoietin receptor superfamily (type I cytokine receptor family) and share 37% homology at the amino acid level. Their respective genes have been mapped to the X chromosome, and *in vitro* expression of IL-13R α 1 and IL-13R α 2 has revealed that they both specifically bind IL-13.⁴⁷⁻⁵² The cDNA for human IL-13R α 1 encodes a 427-amino-acid sequence, including a 26-amino-acid signal sequence. IL-13R α 1 is a 65- to 70-kd glycosylated protein that binds IL-13 with low affinity ($K_d = 2\text{--}10$ nmol/L) by itself, but when paired with IL-4R α , it binds IL-13 with high affinity ($K_d = 400$ pmol/L) and forms a functional IL-13 receptor that signals.⁵⁰ This receptor complex, the type II IL-4/IL-13 receptor, also serves as an alternative receptor for IL-4. The γ_c is not a component of the type II IL-4/IL-13 receptor. There is some evidence that overexpression of the γ_c might affect IL-13 function,⁵³ but the biologic relevance of this is unclear. Overexpression of the γ_c by means of transfection might upset the balance between IL-13R α 1 and the γ_c for IL-4R α . This could result in an increase in IL-4R α / γ_c heterodimers and a compensatory decrease in IL-13R α 1/IL-4R α heterodimers, which would diminish IL-13 signaling. However, the γ_c is not a component of the IL-13 receptor complex.⁵⁴

The interaction between IL-4R α and IL-13R α 1 is completely species specific, as evidenced by the fact that human IL-13R α 1 could associate only with human and not mouse IL-4 α to form a functional receptor.⁵⁵ The open-reading frame of human IL-13R α 1 has 81% nucleotide and 76% amino acid identity with murine IL-13R α 1.^{47,49} The epitopes on IL-13R α 1 for binding IL-4R α must not be conserved between human patients and mice. This is surprising because the epitope on the mouse IL-2R γ_c for associating with human or mouse IL-4R α to generate a signaling type I IL-4R is conserved.⁵⁶ The murine IL-2R γ_c can complex with either human or murine IL-4R α to create a functional type I IL-4R. In contrast, this is not the case for IL-13R α 1. Exploitation of this species specificity might aid in the identification of the epitope or epitopes required for the IL-13R α 1/IL-4R α interaction. Pharmaceuticals targeted specifically to the target residue or residues would allow specific inhibition of IL-13 function while leaving IL-4 signaling intact and might prove beneficial in the treatment of atopic disorders.

IL-13R α 1 is widely expressed and has been demonstrated on nearly every cell tested except human or mouse T cells and mouse B cells, which is consistent with the known functions of IL-13.⁵⁷⁻⁶⁰ On human B cells, expression of IL-13R α 1 has been reported to be modulated by means of activation through CD40 ligand or surface immunoglobulin.^{57,61}

IL-13R α 2

The cDNA for human IL-13R α 2 encodes a 380-amino-acid protein including a 26-amino-acid signal sequence.⁵² It shares 59% amino acid identity with its mouse counterpart.⁶² IL-13R α 2 transcripts have been found in the spleen, liver, lung, thymus, and brain.^{52,62} As described above, expression of IL-13R α 1 and IL-4R α together is sufficient to render cells responsive to IL-13,

and thus IL-13R α 2 is not required for IL-13 function. Expression of IL-13R α 2 *in vitro* resulted in high-affinity binding of IL-13 ($K_d = 250$ pmol/L) but was insufficient to render cells responsive to IL-13, even in the presence of IL-4R α .⁶² This has led to speculation that IL-13R α 2 is a decoy receptor. This has been further supported by the finding that IL-13R α 2 has been found in soluble form *in vivo*,⁵¹ and its overexpression might diminish IL-13 signaling.^{63,64} However, the biologic role of IL-13R α 2 is still not clear. Generation and characterization of IL-13R α 2 gene-targeted mice will be useful in understanding the function of this receptor.

Recently, IL-13R α 2 was shown to exist largely as an intracellular molecule. Large pools of IL-13R α 2 were found intracellularly in cultured monocytes, respiratory epithelial cells, primary respiratory epithelium, and primary human monocytes, supporting that this observation is not restricted to a given cell type but rather appears to be widespread.⁶⁴ This intracellular pool was rapidly mobilized to the cell surface after treatment of cells with IFN- γ . Furthermore, IFN- γ -dependent upregulation of IL-13R α 2 was associated with diminished IL-13 signaling, supporting the hypothesis that IL-13R α 2 acts as a decoy receptor that can regulate IL-13 responses. This represents a novel mechanism by which IFN- γ can regulate IL-13 responses.

Thus the receptor complexes for IL-4 and IL-13 are intertwined systems that are likely regulated at multiple levels, including by differential levels of expression of the various components, by preferential association of certain components, or both.

IL-13 SIGNALING

Consistent with the fact that IL-4 and IL-13 share common subunits, they also share common signaling pathways. Studies in STAT6-deficient mice have revealed that IL-13 signaling uses the JAK-signal transducer and activator of transcription (STAT) pathway and specifically STAT6.^{65,66} Signaling through IL-4R α /IL-13R α 1 is thought to occur through IL-4R α because both IL-4 and IL-13 stimulation of the complex results in activation of signaling intermediates characteristic of IL-4 responses, including phosphorylation of IL-4R α , insulin receptor substrate 2 (IRS-2), JAK1, and Tyk2.^{28,67} IL-4R α contains 5 conserved tyrosine residues, Y497, Y575, Y603, Y631, and Y713, which are all important in signaling through this receptor. Structure-function analyses have revealed that Y497 is part of the IL-4R motif that is necessary for the recruitment of IRS-1 and IRS-2 to IL-4R α after IL-4 stimulation and is critical for IL-4-dependent cell proliferation.⁶⁸ The tyrosines Y575, Y603, and Y631 can act as STAT6 docking sites, and as long as one of the 3 tyrosines remains intact, IL-4-dependent gene induction remains intact.⁵⁶ Tyrosine 713 is part of an immunotyrosine-based inhibitory motif (ITIM) and was recently shown to be important in the negative regulation of IL-4 and IL-13 responses.⁶⁹ We will now review the signaling pathways activated by IL-13.

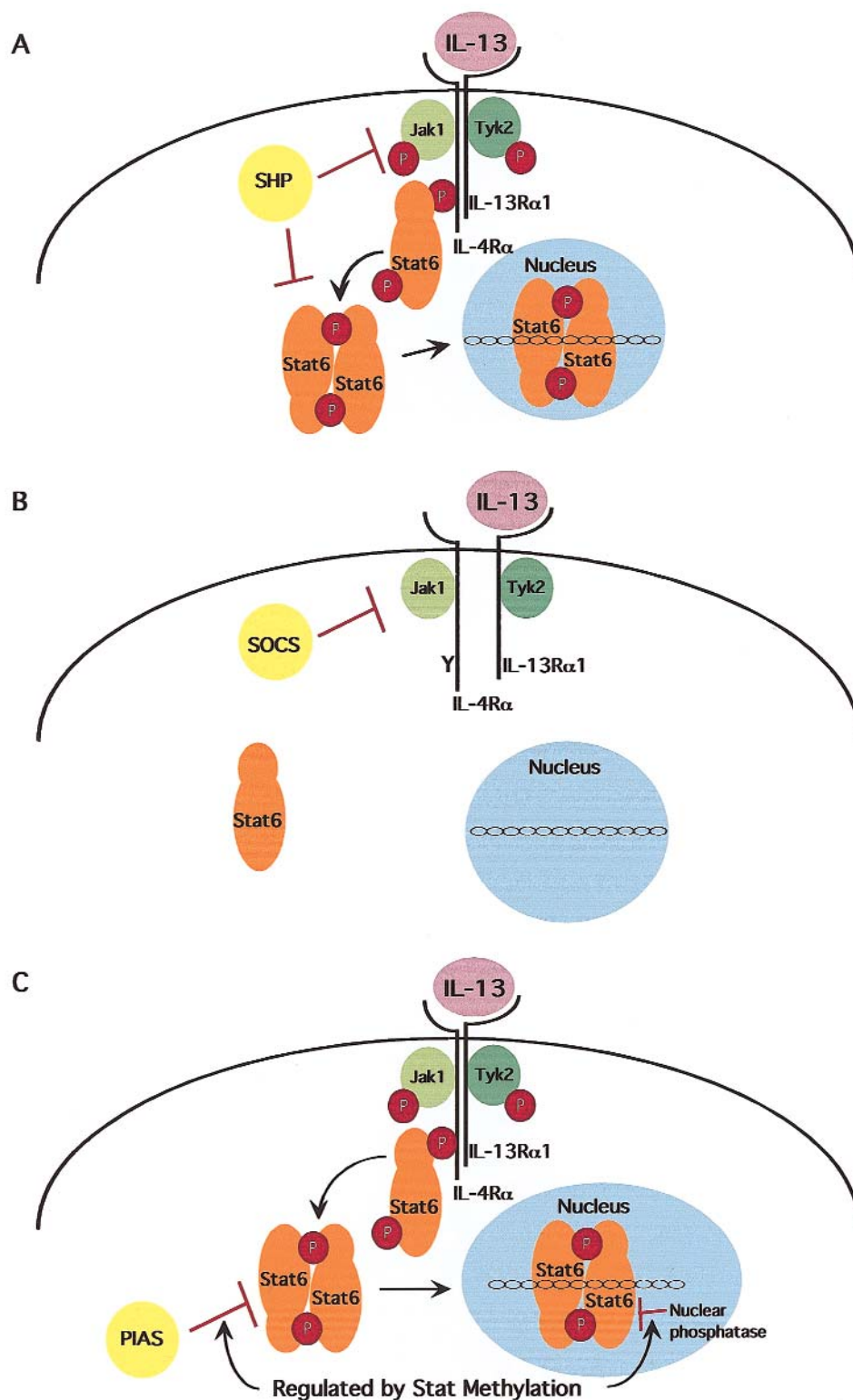


FIG 3. Mechanisms to downregulate IL-13-induced JAK/STAT activation. **A**, SHP. SH2-domain containing tyrosine phosphatases (*SHP*) downregulate IL-13 signaling by dephosphorylating activated JAKs and STATs. **B**, SOCS. Expression of SOCS proteins is induced by cytokine, and then SOCSs bind and inhibit JAKs. They might target the JAKs for proteasomal degradation. **C**, PIAS. Although no PIAS has been yet described for STAT6, PIAS proteins bind to activated STAT dimers and inhibit DNA binding. The schematic overview is based on published observations with STAT1. [A larger version of this illustration is available in the online Journal at (www.mosby.com/jaci).]

JAK/STAT pathway

JAKs are tyrosine kinases that each contains a true catalytic domain and a pseudokinase domain. There are 4 JAKs: JAK1, JAK2, JAK3, and Tyk2. JAK1, JAK2, and Tyk2 are ubiquitously expressed, whereas JAK3 expression is limited to hematopoietic cells.⁶ IL-4R α , γ c, and IL-13R α 1 all contain proline-rich Box-1 regions that bind JAK1, JAK3, and Tyk2, respectively. In hematopoietic cells that express γ c and the associated JAK3, IL-4 binding results in activation of JAK1 and JAK3.^{70,71} In contrast, in nonhematopoietic cells IL-4 treatment results in phosphorylation of JAK1 and Tyk2.^{72,73} This is because in the absence of γ c, IL-4 uses the type II receptor, and IL-13R α 1 binds Tyk2. IL-13 results in activation of JAK1 and Tyk2 in hematopoietic and nonhematopoietic cells.^{67,74,75} Activation of JAKs results in phosphorylation of the cytoplasmic tyrosines in IL-4R α , leading to the recruitment of STAT6 to the receptor, followed by STAT6 phosphorylation and activation.

Activation of STAT6 after receptor engagement involves multiple steps and is dependent on critical structural elements within STAT6. First, association of STAT6 with tyrosine-phosphorylated regions of cytokine receptors occurs through its SH2 domain. Subsequently, STAT6 is phosphorylated on Y641, a residue critical for STAT6 function,⁷⁶ and phosphorylated STAT6 monomers dimerize through their respective amino terminal domains, with Y641 of one monomer associating with the SH2 domain of the other.⁷⁷ Activated STAT6 dimers then translocate to the nucleus, bind specific canonic DNA elements, and initiate transcription of downstream genes. The crystal structure of STAT1-DNA complexes revealed that dimeric interactions between the 2 respective SH2 domains and C-terminal phosphotyrosines were critical for the formation of the DNA-binding region.⁷⁸ In the presence of IL-4 or IL-13, STAT6 activation is maintained indefinitely,^{79,80} and it has been shown that maintenance of STAT6 activity requires ongoing JAK activity and a continuous cycle of activation, deactivation, nuclear export, and reactivation.⁸⁰

The nuclear import requirements for the STAT proteins remain to be identified. Nuclear localization occurs both at the level of nuclear import and nuclear export.⁸¹ No nuclear localization signals have been identified in the STATs; however, a recent report revealed the importance of a leucine-rich nuclear export signal (NES) in STAT1.⁸² NES-mediated nuclear export is mediated through the NES receptor, which was identified as the chromosome maintenance (Crm1) gene.^{83,84} In a recent study nuclear export was shown to be necessary for maintenance of STAT6 activation.⁸⁰

Some STAT molecules, including STAT1, STAT4, and STAT5, can form tetramers through their N-terminal domains, allowing higher affinity binding to recognition sequences in tandem 6. A conserved Trp residue in the N domain is important for tetramer formation. Tetramer formation has not been demonstrated for STAT6.

IRS-1/IRS-2 pathway

IRS-1 and a homologous protein, IRS-2 (also known as 4-phosphotyrosine substrate), are recruited to phosphorylated Y497 of IL-4R α after ligand binding, leading to phosphorylation and activation of IRS-1 and IRS-2.⁸⁵ IRS-1 binds to homologous sequences in the intracellular domains of the insulin and insulin growth factor receptors, and these sequences were found to be critical for signaling.⁸⁶ Similarly, when Y497 was mutated or the surrounding motif was deleted, IRS-1 was not recruited to IL-4R α and was not phosphorylated.⁶⁸ The cells expressing this mutant IL-4R α also displayed a markedly diminished proliferative response to IL-4. Thus Y497 is important for IL-4- and IL-13-dependent proliferation.

Two pathways have been implicated in signaling downstream of IRS-1 and IRS-2: the phosphoinositol 3 (PI3) kinase and Ras/mitogen-activated protein kinase pathways.⁸⁵ After cytokine stimulation, IRS-1 and IRS-2 are phosphorylated and are able to interact with the p85 α subunit of PI3 kinase. The importance of the PI3 kinase in cell proliferation has been further supported by experiments with wortmannin, an inhibitor of PI3 kinase that demonstrated that inhibition of PI3 kinase blocked IL-4-mediated cell survival.⁸⁷ Phosphorylated IRS-1 and IRS-2 also interact with the adaptor protein Grb-2, which associates with SOS, a Ras activator.⁸⁸ The role of the mitogen-activated protein kinase pathway in IL-4R α -mediated signaling is not clear.

Role of IL-13R α 1 and IL-13R α 2 in IL-13 signaling

The precise roles of IL-13R α 1 and IL-13R α 2 in IL-13 signaling and response are not clear. As described above, Tyk2 binds to the box region of IL-13R α 1; however, IL-13R α 1 might have additional yet unknown signaling function. A truncated murine IL-13R α 1 lacking the intracellular domain was not able to mediate IL-13-induced signals or responses, supporting the possibility that IL-13R α 1 is required for signaling.⁸⁹ The cytoplasmic domain of human IL-13R α 1 contains 2 tyrosine residues, Y402 and Y405, which might serve as docking sites for additional signaling intermediates. These tyrosines have been shown to be docking sites for STAT3 *in vitro*, although the biologic relevance of this observation remains to be demonstrated because Y to F mutant IL-13R α 1 receptors mediated IL-13-dependent signaling and growth.^{90,91} Other studies have failed to find activated STAT3 in the nucleus after IL-4 or IL-13 treatment of cells.⁹² Nevertheless, it is striking that the intracellular domain (60 amino acids in length) of IL-13R α 1 is greater than 98% conserved between human patients and mice, differing by only 3 amino acids, and 2 of these 3 differences are conservative changes. This argues that the IL-13R α 1 intracellular domain has an important biologic function. It is possible that the function of the intracellular IL-13R α 1 domain is to allow effective coupling with the signaling IL-4R α chain. The heterodimeric interaction between IL-13R α 1 and IL-

4R α is species specific (ie, human IL-13R α 1 can only associate with IL-4R α and not murine IL-4R α),⁵⁵ and thus the epitopes on IL-13R α 1 responsible for binding IL-4R α must be distinct between the 2 species. Because the human and mouse IL-13R α 1 intracellular domains are nearly identical, these epitopes likely occur in the extracellular domain.

Recently, there is some evidence that IL-13 might have effects that are independent of IL-4R α , suggesting the presence of another distinct IL-13 receptor or receptor subunit.⁹³ Intracellular regions of IL-13R α 1 might serve as docking sites for association of IL-13R α 1 with yet unidentified IL-13 receptors, signaling intermediates, or both or, alternatively, with the other known IL-13 receptor, IL-13R α 2. It is currently not known whether IL-13R α 1 and IL-13R α 2 form a physiologic complex.

As discussed above, IL-13R α 2 is thought to act as a decoy receptor because expression of IL-13R α 2 *in vitro* resulted in high-affinity IL-13 binding but was insufficient to render cells responsive to IL-13, even in the presence of IL-4R α .⁶² IL-13R α 2 has a short cytoplasmic tail (17 amino acids in the human subject) that contains no Box-1 or Box-2 signaling motifs, supporting the hypothesis that it has no signaling function. Both human and murine IL-13R α 2 contain a tyrosine residue in their respective short intracellular domains, but no signaling role has yet been identified for this tyrosine. Recently, it was demonstrated that IL-13R α 2 can mediate internalization of IL-13 independent of IL-13 signaling⁶³ and that this internalization is dependent on a dileucine motif in the transmembrane domain.⁹⁴

REGULATION OF IL-13 SIGNALING: REGULATION OF THE JAK/STAT PATHWAY

Although STAT6 activation in response to IL-4 and IL-13 has been well documented, the molecular mechanisms responsible for the termination of JAK/STAT signaling remain poorly understood. A number of negative regulators of the JAK/STAT signaling pathway have been described, including SH2-containing phosphatases, suppressors of cytokine signaling (SOCS), and protein inhibitors of activated STAT of transcription (PIAS). These are shown schematically in Fig 3.

SH2-containing phosphatases

SH2 domain-containing tyrosine phosphatase 1 (SHP-1) is an intracellular protein tyrosine phosphatase that is widely expressed in hematopoietic cells. It has been shown to be involved in the negative regulation of multiple cytokine receptors, including erythropoietin, IL-2, IL-3, CSF, and IL-4R α .⁹⁵⁻¹⁰¹ SHP-1 has been shown to associate with IL-4R α ^{100,102} and recently was shown to negatively regulate IL-4 responses in pre-B-cell lines derived from *me/me* mice.¹⁰¹ Furthermore, nonspecific inhibition of tyrosine phosphatase activity resulted in constitutive activation of JAK1 and STAT6, supporting a role for phosphatases in the negative regulation of the pathway.¹⁰³ In addition, overexpression of SHP-1 result-

ed in reduced IL-4-dependent STAT6 activation.¹⁰¹ Studies have demonstrated an association of SHP-1 and SHP-2 with the IL-4R α chain.^{100,102} The mechanisms by which these phosphatases inhibit JAK/STAT signaling are unclear. They might bind to receptors and act on STATs, as recently suggested.⁶⁹ Alternatively, SHP-1 has been shown to bind JAK2 directly,⁹⁷ suggesting that the phosphatase acts directly on JAKs.

The ITIM motif I/VxYxxL has been identified in a growing family of inhibitory receptors and plays a critical role in negative regulation of signaling through the receptors.¹⁰⁴ Recently, the sequence containing Y713 in the IL-4R α chain was identified as a functional ITIM.⁶⁹ SHP-1, SHP-2, and SH2-containing inositol phosphatase were all shown to interact with the Y713 putative ITIM sequence, and ablation of this sequence resulted in an enhanced proliferative response to IL-4. The mechanism of this is still unclear because the activation of JAK1 and IRS-2 were not affected by ablation of the ITIM Y713.⁶⁹

Suppressor of cytokine signaling

The first member of this family, cytokine-inducible SH2-containing protein (CIS), was discovered as an immediate early gene induced by multiple cytokines.¹⁰⁵ SOCS proteins were discovered by 3 groups using distinct approaches to search for proteins capable of inhibiting cytokine responses,¹⁰⁶ interacting with JAKs,¹⁰⁷ and containing homology to STAT SH2 domains.¹⁰⁸ Thus SOCSs are also known as JAK2-binding protein, STAT-induced STAT inhibitor, and CIS. There are now 8 members of this family, SOCSs 1 through 7 and CIS, and their expression profiles vary.¹⁰⁹ SOCS proteins form a negative feedback loop whereby SOCS genes are induced after cytokine stimulation and inhibit cytokine signaling.¹¹⁰⁻¹¹² An important feature of SOCS-mediated regulation is that it inhibits multiple pathways, and there is considerable cross-talk.^{109,110} For example, when SOCS-1 is overexpressed in cell lines, it inhibits STAT activation by several cytokines, including IL-4.¹¹³ IFN- γ antagonizes many of the activities of IL-4 and IL-13, and this is mediated by SOCS-1 in a STAT1-dependent fashion.^{111,112} However, characterization of SOCS-1 null mice has shown that SOCS-1 is also a critical regulator of IFN- γ responsiveness.¹¹⁴ Thus SOCS-1 is important in the cross-talk between IFN- γ and the IL-4 and IL-13 pathways.

SOCS-1 has been shown to bind and inhibit JAKs,¹¹⁰ but this might not be true of all SOCS family members. The mechanisms by which the SOCSs function are still not clear. Each of the SOCSs contains an N-terminal domain, a central SH2 domain, and a C-terminal SOCS box, which mediates binding to elongin B/C.^{115,116} It has been hypothesized that binding of elongin B/C to SOCSs might target SOCSs and any associated proteins (eg, JAKs) to the proteasome for degradation.^{116,117} A recent study provided further evidence for this hypothesis, whereby SOCS-mediated inhibition of cytokine signaling required an active proteasomal degradation pathway.¹¹⁸

Protein inhibitor of activated STAT

Another important family of proteins in the regulation of the JAK/STAT pathway is the PIAS family of proteins, which have recently been described and have specificity for some STAT family members.^{119,120} These proteins bind specifically to phosphorylated STAT dimers and prevent them from binding DNA.¹²¹ The PIAS proteins are constitutively expressed, and little is known about their regulation. However, recent studies have demonstrated that STAT1 function is modulated by means of methylation of a critical arginine residue at position 31.¹²² Arg31 is conserved among the STAT molecules, and methylation is likely generally important for STAT function. The mechanism of this methylation-dependent modulation appears to be regulation at the level of STAT1-PIAS1 association. PIAS1 binds to STAT1 dimers and prevents STAT1 DNA binding. Methylation of STAT1 reduces the ability of it to associate with PIAS and thus increases STAT1 DNA-binding activity.¹²² No PIAS has yet been identified for STAT6, the STAT activated by IL-4 and IL-13.

Several possibilities exist as to the fate of an activated STAT6 molecule once it has completed its role in IL-4- or IL-13-dependent signal transduction. One possibility is that STAT6 is ubiquitinated and regulated by means of proteasomal degradation. Indeed, inhibitors of proteasome degradation have been shown to prolong STAT1 activation^{123,124} and STAT6 activation.¹²⁵ Thus a constant cycle of activation, degradation, and de novo protein synthesis might be required to maintain a prolonged STAT6 response. A second possibility is that activated STAT6 in the nucleus is deactivated by means of dephosphorylation through the action of a specific phosphatase. Several studies have implicated tyrosine phosphatases in the regulation of STAT signaling.^{124,126-128} Consistent with this possibility, studies examining STAT1 have shown that activated STAT1 disappears from the nucleus within 60 minutes and that removal of the activated STAT1 is dependent on a protein tyrosine phosphatase.¹²⁴ Recently, a nuclear isoform of T cell-protein phosphatase (also referred to as TcPTP) was identified as the tyrosine phosphatase responsible for STAT1 dephosphorylation in the nucleus.¹²⁹ Interestingly, another recent study demonstrated that dephosphorylation of STAT1 by a nuclear isoform of T cell-protein phosphatase (or TcPTP) is regulated by arginine methylation of STAT1 and that this regulation is dependent on PIAS.¹³⁰ These data are consistent with a model whereby methylation increases association of STAT1 with PIAS with a concomitant decrease in binding of STAT1 to TcPTP and thus delayed dephosphorylation of STAT1. Such a model would also implicate a specific nuclear protein tyrosine phosphatase in STAT6 deactivation. The deactivated STAT6 molecule could then be degraded or shuttled back to the cytoplasm, where it could be reactivated by means of tyrosine phosphorylation.

The multiple levels of regulation along the JAK/STAT activation cascade underscore the importance of this

pathway, and it is likely that the degradation and recycling of these mediators is also tightly regulated.

Regulation of the IRS-1/IRS-2 pathway

The IL-4R α -associated kinase Fes¹³¹ was recently shown to be important in regulation of the IRS-1/IRS-2 pathway.¹³² Fes is a tyrosine kinase expressed in hematopoietic cells, and overexpression of kinase-inactive Fes blocks IL-4-dependent activation of IRS-2 and its downstream association with PI3 kinase but has no effect on STAT6 activation.¹³² Interestingly, Fes appears to be activated by JAK1 because Fes was not activated in JAK1-deficient cells. These data support a role for Fes as a signaling intermediate between JAK1 and phosphorylation of IRS-1 and IRS-2 and thus subsequent activation of PI3 kinase. Interestingly, Fes has also been implicated as a regulator of JAK/STAT signaling. STAT activation was enhanced in macrophages derived from *c-fes*^{-/-} mice,¹³³ suggesting that Fes might be a negative regulator of STAT.

GENETIC VARIANTS OF IL-13 AND IL-4R α

Genetic variants of IL-13 that are associated with asthma and atopy have been found both in the promoter and coding regions.¹³⁴⁻¹³⁷ The coding variant results in a substitution of an arginine with a glutamine at position 130 (numbering includes the 20-amino-acid signal sequence). This variant has been found to be associated with asthma, increased IgE levels, and atopic dermatitis in Japanese and European populations.^{134,136,137} In a recent study the mechanism by which this variant might predispose to asthma was investigated.¹³⁸ The investigators found that the IL-13 Q130 variant displayed somewhat enhanced stability compared with the wild-type IL-13 and that this might result from a slightly higher affinity of the IL-13 variant for IL-13R α 2. Consistent with these observations, they found higher median serum IL-13 levels in patients homozygous for the Q130 IL-13 variant when compared with nonhomozygous patients.

The gene encoding IL-4R α represents an ideal candidate gene for atopy susceptibility because of its pivotal role in both IL-4 and IL-13 signaling, its key role in allergic inflammation by promoting IgE production and T_H2 cell development, and its location on chromosome 16, which has been linked to asthma.¹³⁹ Eight naturally occurring allelic variants of IL-4R α have been reported,^{102,140-142} and several of these have been associated with the prevalence of atopy^{102,141-143} and the severity of asthma.¹⁴⁴ Two of the allelic variants of the gene encoding IL-4R α that have been associated in multiple studies with asthma and atopy are the I75V and Q576R polymorphisms (numbering including the 25-amino-acid signal peptide).^{102,143} Both the Q576R and I75V polymorphisms are common and occur in combination in the general population, and thus it is important to examine the functional consequences of these polymorphisms alone and in combination. We recently reported that although neither the Q576R nor

the I75V variants alone affected IL-4-dependent CD23 expression, the combination of V75R576 resulted in enhanced sensitivity to IL-4.¹⁴⁵ Furthermore, the association of V75/R576 with atopic asthma was greater than that of either allele alone, and the association of R576 with atopic asthma was dependent on the coexistence of V75.

Thus it is critical to study the effects of snps in combination because the functional significance of a given snp might only be evident in a specific setting of additional snps in the same or different genes. Furthermore, small functional changes in gene products that act along a common pathway might have a significant effect. There is evidence for this from a recent genetic study demonstrating interactive genetic effects between snps in IL-4R α and the IL-13 promoter.¹⁴⁶ A relatively small change in the production of IL-13 caused by a promoter polymorphism coupled with a second small functional change in its receptor, IL-4R α , might result in a combined change that is biologically significant, although neither alone is significant. Additional studies examining the functional and genetic contributions of multiple snps in series acting on a common pathway are needed to further our understanding of these events.

IL-13 RECEPTOR/SIGNALING PATHWAYS AS A TARGET FOR THERAPEUTIC INTERVENTION

IL-13 regulates a variety of functions in hematopoietic and nonhematopoietic cells and has been shown in clinical studies to be associated with the development of atopic disorders, including atopic dermatitis,^{147,148} allergic rhinitis,¹⁴⁹ and asthma.¹⁵⁰⁻¹⁵³ It has been demonstrated to play a pathogenic role in the development of bronchial asthma independent of IL-4.³²⁻³⁴ Thus IL-13 and its receptor and signaling pathways are an attractive target for immunotherapy. Currently, studies are underway to evaluate the clinical potential of IL-13 antagonists, including soluble IL-13R α 2. The optimal strategy would be to block IL-13, but not IL-4, responses. IL-13 receptors are also expressed on a variety of tumor cell lines,^{154,155} and IL-13 has been implicated in the pathogenesis of malignancies, such as Hodgkin disease, in which IL-13 acts as an autocrine growth factor for Reed-Sternberg tumor cells.¹⁵⁶ Thus IL-13 antagonists might also be useful in the treatment of malignancies.

CONCLUSIONS

IL-13 is a critical mediator of allergic inflammation and contributes directly to airway hyperreactivity. As such, it is one of the most attractive, novel potential targets for therapeutic intervention in the treatment of asthma. Studies are already underway evaluating soluble IL-13 receptors. Although much is now known about this cytokine and its signaling pathways, as discussed in this review, important pieces of the puzzle remain unknown.

One of the biggest questions that remains is how IL-13 induces the effects that IL-4 does not. Because both IL-4 and IL-13 transmit their signals through the IL-4R α , the mechanism by which IL-13 results in downstream effects that are not observed with IL-4 is a mystery. It is possible that additional IL-13-specific signaling molecules or receptor proteins exist. Alternatively, differences in IL-4 and IL-13 effects might be due to differences in the kinetics of their production or half-lives locally. Finally, the function of IL-13R α 2 is still unclear, and this receptor might play a yet unrecognized role in IL-13 signaling. Identification of the mechanisms that account for the IL-13 effects that are not seen with IL-4 will allow the development of compounds to target IL-13 independently of IL-4. Furthermore, this information will allow investigators to better evaluate potential drugs. In any case, it is clear that the intense ongoing investigation in this field will likely yield exciting new targets for therapy for allergy and immunology patients.

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