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Untangling the Complex Web of IL-4– and IL-13–Mediated Signaling Pathways

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Abstract

Unraveling the exact signaling events mediating the distinct functions of the T cell–derived cytokines interleukin-4 (IL-4) and IL-13 has been challenging because they are structurally similar and share a functional signaling receptor chain. A study now proposes a potential molecular mechanism to explain the functional differences between IL-4 and IL-13 that involves the ability of IL-4, but not IL-13, to effectively activate the insulin receptor substrate–2 (IRS-2) signaling cascade through binding to its receptor. A better understanding of the interactions of IL-4 and IL-13 with their cognate receptors may facilitate the development of therapies without unintended side effects.

The ongoing epidemic of allergic asthma in the developed world lends urgency to the quest to understand its pathogenesis. There is agreement that asthma arises from aberrant immune responses to airborne substances in genetically susceptible individuals. Interleukin-4 (IL-4) and IL-13, which are produced by activated CD4⁺ T cells, are critical for the promotion of allergic responses (1, 2). Although both cytokines independently elicit all manifestations of allergic asthma (1–4), they mediate distinct physiological functions in vivo. IL-4 is primarily involved in promoting the differentiation and proliferation of T helper 2 (T_H2) cells and the synthesis of immunoglobulin E (IgE), whereas IL-13 has a critical role in mediating airway hyperresponsiveness (AHR) and mucus hypersecretion, the elements of asthma most closely linked to the manifestations of the disease (1, 2). The importance of these pathways to disease expression is illustrated by strong associations between overzealous T_H2 immune responses in asthmatic individuals and mutations in critical regulatory regions of the genes encoding the IL-4 receptor α -chain (IL-4R α) (5) and IL-13 (6). Elucidation of the mechanisms by which these cytokines mediate their separate or overlapping functions has proven difficult because they can both signal through a shared receptor chain (7, 8). Heller and colleagues now provide a potential molecular mechanism to explain functional differences between IL-4 and IL-13 that involves the ability of IL-4, but not IL-13, to

effectively activate the insulin receptor substrate-2 (IRS-2) signaling cascade through binding to its type I receptor, which leads to enhanced transcription of a subset of genes associated with alternatively activated macrophages (9).

Although multiple hypotheses have been advanced to explain the relative differences in the contributions of IL-4 and IL-13 to allergic inflammation, the exact mechanisms involved remain obscure. One difference between the two cytokines is that IL-4 binds to two distinct receptor complexes, whereas IL-13 only binds to one of these complexes (10-12). Specifically, IL-4 binds to the IL-4R α chain, the functional receptor chain in both the type I receptor, which is a heterodimer of IL-4R α and the γ_c chain, and the type II receptor, which is a heterodimer of IL-4R α and IL-13R α 1. IL-13, in contrast, does not bind to IL-4R α directly but binds to IL-13R α 1 and, as a result, can only activate the type II IL-4R (Fig. 1). IL-13 also binds to IL-13R α 2 with high affinity, but this interaction is not thought to activate allergy-promoting signaling pathways (13). Although IL-4R α is ubiquitously present, γ_c but not IL-13R α 1 is found on T cells, natural killer (NK) cells, basophils, mast cells, and most mouse B cells (most human B cells express both γ_c and IL-13R α 1). Consequently, IL-4, but not IL-13, promotes the differentiation of naïve T cells into T_H2 cells, and IL-4 is much more important than IL-13 for the induction of mouse IgE responses (11, 14). Some bone marrow-derived cells, including macrophages and dendritic cells, express both γ_c and IL-13R α 1 and consequently respond to both IL-4 and IL-13. Differences in the relative abundance of these two receptor subunits on different subpopulations of these cells may account, in part, for their relative responsiveness to IL-4 versus IL-13. IL-13R α 1, but little or no γ_c subunit, is found on most non-bone marrow-derived cells, including smooth muscle and epithelial cells; consequently, IL-4 has no inherent advantage over IL-13 in stimulating these cells.

Because IL-4 and IL-13 can signal through distinct receptors, it can be postulated that they may be able to activate different signal transduction pathways. Indeed, γ_c activates the tyrosine kinase Janus kinase 3 (JAK3), whereas IL-13R α 1 activates Tyk2 and JAK2 (11, 12). Activated JAKs mediate the phosphorylation of the cytoplasmic tail of IL-4R on conserved tyrosine residues that serve as docking sites for proteins containing Src homology 2 (SH2) domains. Three closely clustered tyrosine residues serve as docking sites for signal transducer and activator of transcription 6 (STAT6), a transcription factor selectively coupled to the IL-4R α chain. The binding of IL-13 to IL-13R α 1 also activates STAT6 because the IL-13:IL-13R α 1 complex binds with high affinity to IL-4R α (15). Consistent with the ability of each of these cytokines to activate STAT6 signaling, the majority of the physiological manifestations of allergic disorders, including T_H2 cell differentiation, AHR, mucus cell metaplasia, and IgE synthesis, are STAT6-dependent. However, antigen-induced eosinophilia is only partially STAT6-dependent, which suggests that other signaling pathways may also be activated in the context of allergic inflammation (16). In support of a role for STAT6-independent signaling pathways in allergic inflammation, exposure of mice to antigen induces the expression of both STAT6-dependent and -independent genes (17).

In addition to STAT6, IL-4 recruits and activates IRS-2. Structure-function analyses have revealed that a tyrosine residue [Tyr⁴⁹⁷, part of the insulin/IL-4R motif (I4R)] on the transmembrane domain of IL-4R α is necessary for the docking of IRS-2 to IL-4R α after

IL-4R α has been activated by IL-4 (18). JAK1 and JAK3 then phosphorylate IL-4R α -bound IRS-2. The activation of IRS-2 leads to the activation of phosphoinositide 3-kinase (PI3K) and the downstream protein serine/threonine kinase Akt (19), a pathway that is thought to mediate growth and survival signals in many cell types. Indeed, this pathway is important in IL-4-mediated growth in cells exclusively expressing the type I IL-4R (NK cells, T cells, and B cells) (19, 20). However, little else is known about the role of IRS-2 in IL-4- or IL-13-mediated regulation of other aspects of allergic inflammation, partly because the PI3K-Akt pathway is induced by many other ligands. However, evidence presented by Heller and colleagues (9) suggests that IRS-2 signaling may play a previously unrecognized role in the activation of gene expression in macrophages. Specifically, Heller *et al.* explored the potential roles of IRS-2 and STAT6 signaling pathways in myeloid cells that expressed either both the type I and type II IL-4 receptors or only the type II receptor. They found that IL-4 and IL-13 activated STAT6 similarly in cells expressing both receptors, with IL-4 being the more potent cytokine. In contrast, IL-4, but not IL-13, effectively induced the phosphorylation of IRS-2 in these cells. Importantly, the stimulation of cells expressing only the type II receptor by IL-4 or IL-13 resulted in minimal activation of IRS-2, suggesting that IL-4 activates IRS-2 predominantly through the type I receptor. This was confirmed by experiments with bone marrow-derived cells from γ_c -deficient mice. Although the precise mechanism by which stimulation of the type I IL-4R by IL-4 activates IRS-2 is unknown, other cytokine receptors containing γ_c also phosphorylate IRS-2, which suggests that the critical signal arises from the γ_c chain. Because JAK3 is preferentially recruited by other receptors containing γ_c , JAK3 may preferentially activate the I4R motif. The lack of activation of JAK3 by the type II IL-4R may explain the weak activation of IRS-2 by IL-13. The greater relative abundance of IL-4R α relative to that of IL-13R α 1 in cells expressing both receptors probably explains the greater potency of IL-4 for the activation of STAT6, given that the potencies of IL-4 and IL-13 to activate STAT6 in cells expressing only the type II receptor were equivalent.

To explore the functional consequences of IL-4-mediated activation of the type I receptor in bone marrow-derived macrophages, Heller and colleagues investigated the expression of a subset of genes traditionally associated with alternatively activated macrophages. These macrophages, in contrast to classically activated macrophages, are activated by IL-4 and IL-13 rather than interferon- γ (IFN- γ) and play an important role in wound repair and immunity against multicellular pathogens. Alternatively activated macrophages also serve to dampen harmful immune responses elicited by T_H1 cytokines. They report that exposure of bone marrow-derived macrophages to IL-4 increased the expression of *arginase 1*, *chitinase-like-3* (also known as *YM-1*), and resistin-like molecule- α (RELM- α), also known as found in inflammatory zone 1 (FIZZ1), in a γ_c -dependent manner. Although these results suggest that IL-4-stimulated expression of these genes is IRS-2-dependent, they do not directly demonstrate this. In fact, the expression of only one of these genes (*FIZZ1*) was dependent on the PI3K pathway, suggesting either that IRS-2 activates additional downstream pathways that regulate the expression of these genes or that these genes are regulated by other, as yet undescribed, type I IL-4R-dependent downstream signaling pathways.

Consistent with the hypothesis that the expression of genes associated with alternatively activated macrophages is type I IL-4R-dependent, two groups have shown that allergen-mediated induction of these same genes is IL-13R α 1-independent in vivo (21, 22). Although the exact role of alternatively activated macrophages in the allergic diathesis is not well understood, the disassociation of the induction of these genes from allergen-induced AHR and mucus cell changes in IL-13R α -deficient mice suggests that alternatively activated macrophages do not drive these phenomena. Interestingly, one of these genes, *FIZZ1*, has an inhibitory role in allergic inflammation (23). Likewise, members of the chitinase family (AMCase) to which YM-1 belongs have been shown to inhibit allergic inflammation (24). Along these lines, we have shown that IL-4 inhibits the expression of a panel of IL-13-dependent genes, including *SPRRA* and *Ca2T6*, in vivo (25). IL-4-dependent suppression of the expression of these genes is mediated through non-B, non-T cells that are activated by IL-4 signaling through the type I receptor, inasmuch as this effect was γ_c -dependent. Consistent with a negative role for signals mediated through the I4R:IRS-2 pathway in allergic inflammation, Blaeser and colleagues (26) explored the role of I4R in allergic inflammation in mice with a germline point mutation that changed the motif's effector tyrosine residue into phenylalanine (Tyr⁵⁰⁰→Phe⁵⁰⁰). This mutation abrogates the phosphorylation of IRS-2 but has no effect on the activation of STAT6. However, the Tyr⁵⁰⁰→Phe⁵⁰⁰ mutation is associated with increases in each of the cardinal features of allergic disease (IgE synthesis, airway responsiveness, tissue eosinophilia, and mucus production) in vivo, which supports the contention that IL-4-mediated activation of IRS-2 pathways through the type I receptor may activate inhibitory pathway(s). The potential importance of the I4R motif in human asthma has been highlighted by the strong association between a polymorphism in the human I4R motif (Ser⁵⁰³→Pro⁵⁰³) and asthma and AHR (27). Further studies are clearly needed to explore the full extent of functions mediated through IL-4-dependent activation of the type I receptor and IRS-2 signaling pathways in allergic inflammation.

Although the ability of IL-4 to signal through the type I receptor may explain the functions of IL-4 in cells that express the type I receptor, it still remains to be determined how IL-13 dominates in some in vivo responses when IL-4 and IL-13 use the same type II IL-4R complex in nonhematopoietic airway cells. The most straightforward difference is in the quantity of each cytokine produced during a T_H2-dependent response; generally, IL-13 is produced in considerably greater quantities, by more cell types, and for a longer period of time than is IL-4. This has been shown in mouse models of airway disease (22) and in biopsies of the airways of human asthmatics (28). This difference probably accounts for much of the greater effector function of IL-13 as compared to IL-4. However, even the large quantities of IL-4 produced in the lungs of IL-4 transgenic mice induce less AHR than is induced in IL-13 transgenic mice (3).

Determination of the crystal structures of the IL-4R receptor chains bound to their ligands has revealed how IL-4 and IL-13 may stimulate the same receptor chains very differently. Specifically, the extracellular portion of the IL-13R α 1 chain has a top-mounted Ig domain that seems to enhance the binding efficiency of the IL-13:IL-13R α 1 complex to IL-4R α , compared to that of the IL-4:IL-4R α complex to IL-13R α 1 (29). Based on these findings, a

model has been postulated by LaPorte and co-workers (29) that predicts that IL-4R α binds to IL-4 with high affinity and thus can capture this cytokine at low concentrations. However, IL-4-stimulated assembly of the complete complex is inefficient; so when receptor chains are limiting in abundance, responses to IL-4 are blunted. In contrast, IL-13 binds to IL-13R α 1 with intermediate affinity, and high concentrations of IL-13 are required to assemble the complex, but the interaction of IL-13:IL-13R α 1 with IL-4R α is efficient in promoting assembly of the complete signaling complex even when the abundance of IL-13R α 1 is limiting. Studies comparing the influence of IL-4R α concentration on responses to IL-4 and IL-13 in macrophages expressing different quantities of these receptor chains support this model (30). In the context of allergic inflammation, the abundance of IL-13R α 1 is substantially elevated after exposure to allergen, whereas that of IL-4R α is relatively constant (31). Thus, in the face of higher concentrations of IL-13 in the allergic lung and the greater abundance of IL-13R α 1 as compared to that of IL-4R α , IL-13 has the distinct advantage.

Although it is clear that the regulation of allergic responses by IL-4 and IL-13 is extremely complex, a picture is emerging in which IL-4 mediates many specific functions, including fine-tuning the T_H2 immune response through its ability to initiate (T_H2 cell proliferation), perpetuate (T_H2 cytokine production, IgE synthesis, and eosinophil and alternatively activated macrophage activation), or shut off (suppression of IL-13-mediated processes) the allergic response through the activation of multiple signaling pathways (STAT6 and IRS-2), downstream of its type I receptor. On the other hand, IL-13 preferentially drives the development of the pathological features of the disease manifested by non-bone marrow-derived cells, because of differences in the quantities of IL-4 and IL-13 produced, the distribution of type II IL-4Rs in nonhematopoietic structural cells in the airways, and the low abundance of IL-13R α 1 relative to that of IL-4R α at the site of inflammation. Further studies are particularly needed to examine the contribution of IL-4 and IL-13 signaling pathways in individual cell types involved in the allergic diathesis. With such knowledge in hand, exploitation of the separate and overlapping functions of these signaling pathways in drug design should greatly inform the development of safe, effective antagonists of cytokines and cytokine receptors for the treatment of allergic disorders.

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Fig. 1.

Schematic representation of the IL-4 and IL-13 receptor signaling pathways. Both IL-4 and IL-13 signal predominantly or entirely through the IL-4R α polypeptide, which is a component of two IL-4Rs: the type I receptor, composed of IL-4R α and γ C, and the type II receptor, composed of IL-4R α and IL-13R α 1. IL-4 signals through both IL-4Rs, whereas IL-13 signals only through the type II IL-4R. IL-13 also binds to the IL-13R α 2 chain, which does not contain a transmembrane signaling domain and is thought to act as a decoy receptor. The binding of IL-4 and IL-13 to their respective partners results in receptor dimerization of either the type I or the type II receptor complexes, which activates the JAKs associated with the cytoplasmic tails of the receptors. Type I receptors activate JAK1 and JAK3, whereas type II receptors activate JAK1, JAK2, and Tyk2. Tyrosine residues in the IL-4R α chain become phosphorylated and act as docking sites for signaling molecules. The first tyrosine residue interacts with protein-binding domains (PTBs) such as IRS proteins. Phosphorylated IRS binds to the p85 subunit of PI3K and to the adaptor protein growth factor receptor-bound protein 2 (Grb2). This pathway is linked to the proliferation of T_H2 cells and the induction of genes associated with alternatively activated macrophages in response to IL-4. The second through fourth tyrosines of IL-4R α interact with the SH2 domain of STAT6. Phosphorylated STAT6 dimerizes, migrates to the nucleus, and binds to the promoters of IL-4- and IL-13-responsive genes such as those associated with IgE class switching. STAT6 is dephosphorylated by various SH2 domain-containing phosphatases. IL-13 signaling through the type II receptor in nonhematopoietic cells may also activate STAT3 through the tyrosine residues on IL-13R α 1. Hematopoietic cells such as T and B cells express only the type I receptor, whereas cells of the myeloid lineage such as monocytes, macrophages, and fibroblasts express both type I and type II IL-4Rs. Nonhematopoietic cells such as smooth muscle cells and epithelial cells predominantly

express the type II receptor. The separate functions of IL-4 and IL-13 arise from a combination of factors, including the ability of IL-4 alone to drive the proliferation of T_H2 cells, IgE synthesis, and gene expression in alternatively activated macrophages through binding to its type I IL-4R. IL-13, but not IL-4, signaling through type II receptors preferentially drives the development of the pathological features of disease because of differences in the amount of IL-13 produced and the higher abundance of IL-13R α 1 as compared to that of IL-4R α at the site of inflammation. Because the recruitment of eosinophils is not driven by the type II receptor, it is assumed that this occurs through the type I receptor, but the mechanisms involved are unknown.