# Decoy Receptors in the Regulation of T Helper Cell Type 2 Responses

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Th2-driven responses are instrumental in disease processes including allergies, asthma, and helminth infection, and are characterized by the production of the cytokines IL-4, IL-5, IL-9, and IL-13. These cytokines form a complex network of molecular and cellular interactions that mediate protective immunity not only to worm infection, but also to induce inappropriate inflammatory responses to allergic challenge. Given the clinical importance of these molecules, considerable effort has gone into attempting to identify the relative contributions of the major Th2 cytokines to such disease processes. It has become apparent that Th2 responses are highly complex and might be regulated at many levels through a multitude of pathways, including temporal and spatial regulation of both cytokine and cytokine receptor transcription and translation, so as to initiate an appropriate defense mechanism as well as return to a basal level once the infection has been controlled. Thus, during an immune response certain signals lead to the upregulation of cytokine secretion by specific cells whereas others lead to the expression of the cognate receptors of these ligands by responding cells, resulting in cellular activation where ligand and receptor expression coincide. However, this model is complicated by the existence of multiple cytokine receptors with overlapping binding specificities. It is important, therefore, not only to determine the roles of the individual cytokines, but also the functions mediated by their receptors.

IL-13 has proven to be an extremely important immunoregulator and its direct roles in the generation of disease pathology has triggered the search for therapeutics capable of blocking the actions of IL-13 in vivo. Recent investigations have addressed the functional biology of IL-13 using in vivo models with defined Th2 responses. Complementary studies using IL-13 antagonists and IL-13–deficient mice have demonstrated that ablating IL-13 activity profoundly inhibits the pathophysiology of asthma (1–3) and impairs the expulsion of parasitic gastrointestinal helminths (4, 5). Similarly, overexpression of IL-13 in transgenic mice

has highlighted the potentially detrimental responses initiated by this cytokine. As overexpression of IL-13 in mice leads to a broad disease phenotype it is important that in normal mice, and presumably in man, the levels of IL-13 are tightly controlled.

The complexity of receptor usage and the potential diversity of signaling pathways combine with the temporal and spatial expression of the individual ligands to create a diversity of possible responses. The receptor components that interact with IL-13 are members of the haematopoietin receptor family and display the complexity and promiscuity typical of this family. Indeed, analysis of IL-4 and IL-13 receptor usage explains many aspects of the overlapping biological responses induced by these related cytokines (Fig. 1). Two IL-13 binding chains have been identified, IL-13R$\alpha$1 and IL-13R$\alpha$2, and these are members of the class I cytokine receptor family. The main structural difference between the two IL-13 receptors is that the IL-13R$\alpha$1 chain has a longer intracellular domain than IL-13R$\alpha$2. IL-13R$\alpha$1 is a low affinity IL-13 binding chain (kD $\sim$4 nM) that requires the recruitment of IL-4R$\alpha$ into a receptor complex for the formation of a high affinity IL-13 receptor (kD $\sim$30 pM) and the initiation of signal transduction (6, 7). Although both IL-4 and IL-13 can cross-compete for IL-4R$\alpha$ when it forms part of the IL-4R$\alpha$–IL-13R$\alpha$1 complex, only IL-4 binds directly to IL-4R$\alpha$ (8). As a consequence, the IL-4R$\alpha$–IL-13R$\alpha$1 complex was also identified as a functional IL-4 receptor (9). Although the IL-13R$\alpha$1–IL-4R$\alpha$ does not have an intrinsic kinase domain it does initiate a Janus kinase/signal transducer and activator of transcription signaling cascade resulting in the activation of signal transducer and activator of transcription 6 (10). Further differential signaling pathways can be envisaged for the IL-4R because IL-4 binding may recruit IL-13R$\alpha$1 or IL-2R$\gamma$c into its active receptor complex (11, 12). The promiscuous IL-2R$\gamma$c chain, found in the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors, does not appear to be a functional component of the IL-13 receptor (13). IL-13R$\alpha$2 binds IL-13 with high affinity (kD $\sim$450 pM) without the presence of additional receptor chains (14–16) and has been engineered to act as a soluble antagonist of IL-13 function (15). Although expressed at the cell surface, the function of IL-13R$\alpha$2 as a signaling molecule

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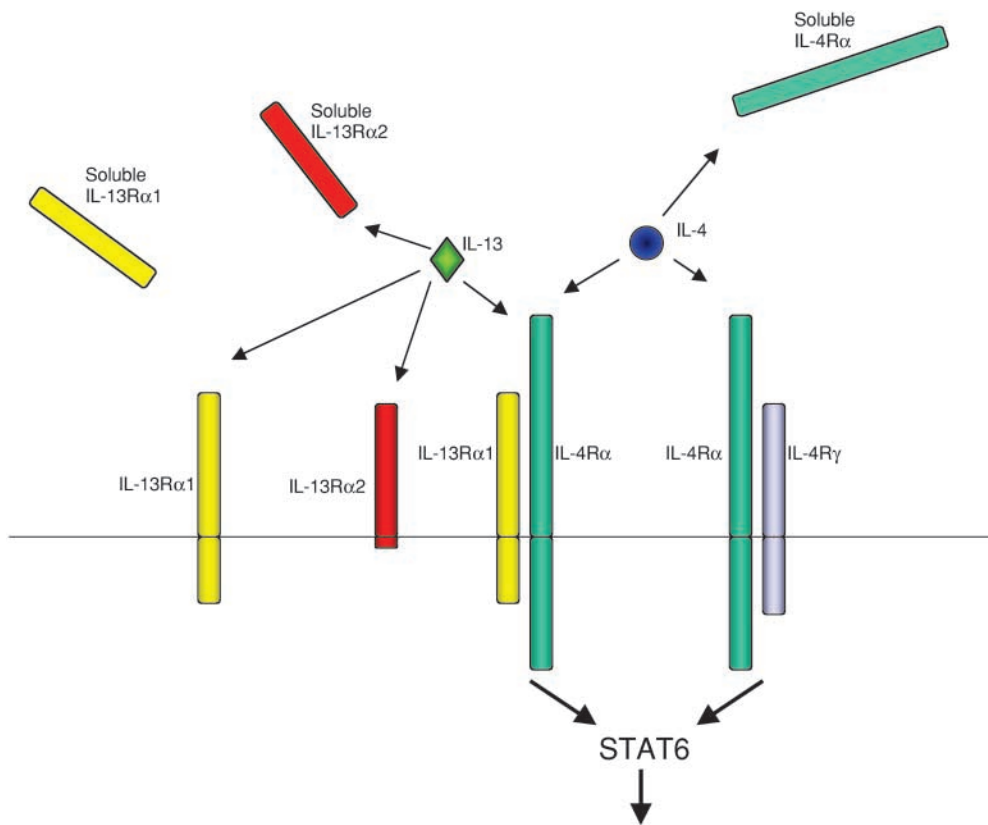
**Figure 1.** Schematic representation of IL-13 and IL-4 receptors.

remains uncertain. Indeed, it has been suggested that IL-13Rα2 may function as an inhibitor of IL-13 activity and the existence of a naturally occurring soluble form of mIL-13Rα2 protein in serum may facilitate this function (16). The complex relationship between the receptor chains of IL-4 and IL-13 represents a functionally important but poorly understood mechanism in the regulation of Th2 responses. In this issue, Wood et al. (17) and Chiaramonte et al. (18) present compelling evidence for IL-13Rα2 acting as a decoy receptor and thereby regulating the magnitude of Th2 responses.

*IL-13Rα2–deficient Mice.* Wood et al. (17) have generated an IL-13Rα2–deficient mouse line to study the impact deletion this molecule has on immune function. Significantly, naive IL-13Rα2$^{-/-}$ animals provide the first formal evidence for IL-13Rα2 acting as a decoy receptor in vivo. Consistent with IL-13Rα2 being a decoy receptor, the IL-13Rα2$^{-/-}$ mice exhibit phenotypic similarities to transgenic mice engineered to overexpress IL-13, including elevated IgE and reduced levels of macrophage-derived IL-12 (19, 20). There are differences, however, notably the increases in the IgA, IgG2a, and IgG2b in the IL-13Rα2$^{-/-}$ mice. Importantly, because these data are from naive mice they imply that expression of the IL-13Rα2 chain is required for regulating even the basal level of IL-13 activity. The article also raises some intriguing questions regarding the role of IL-13Rα2 in regulating the levels of circulating and tissue IL-13. Interestingly, Wood et al. (17) report that naive IL-13Rα2$^{-/-}$ mice have greatly reduced levels of se-

rum IL-13 when compared with IL-13Rα2$^{+/+}$ mice. By contrast, levels of IL-13 were significantly elevated in lung and liver tissues of IL-13Rα2$^{-/-}$ mice compared with IL-13Rα2$^{+/+}$ mice. In an accompanying article in this issue, Chiaramonte et al. (18) also report on the regulation of IL-13 by IL-13Rα2. An important feature of this study was that by adding exogenous IL-13Rα2-Fc, the authors induced a huge increase in the levels of serum IL-13 (18). It is clear that the presence or absence of IL-13Rα2 not only profoundly modulates the levels of IL-13, but also apparently influences its distribution between serum and tissues, raising the question of how this decoy receptor is working. Previous experiments with cell lines have indicated that overexpression of IL-13Rα2 at the cell surface is capable of making the cells unresponsive to IL-13 activation (21, 22). However, two pieces of information presented in the articles in this issue imply that soluble IL-13Rα2 is also responsible for regulating the levels of serum IL-13. First, in the naive mice, the absence of IL-13Rα2 resulted in a marked decrease in the levels of circulating IL-13 but high levels of IL-13 in the tissues (17). This may indicate that the decoy receptor acts as a carrier for IL-13, however, the consequences of this interaction are not clear because ligand/receptor binding may serve to facilitate ligand preservation or destruction. Second, it is noteworthy that treatment with the soluble IL-13Rα2-Fc antagonist also resulted in an increase in circulating IL-13 (18). However, in this case it is unclear how the presence of the Fc domain alters the function of the native IL-13Rα2 molecule because
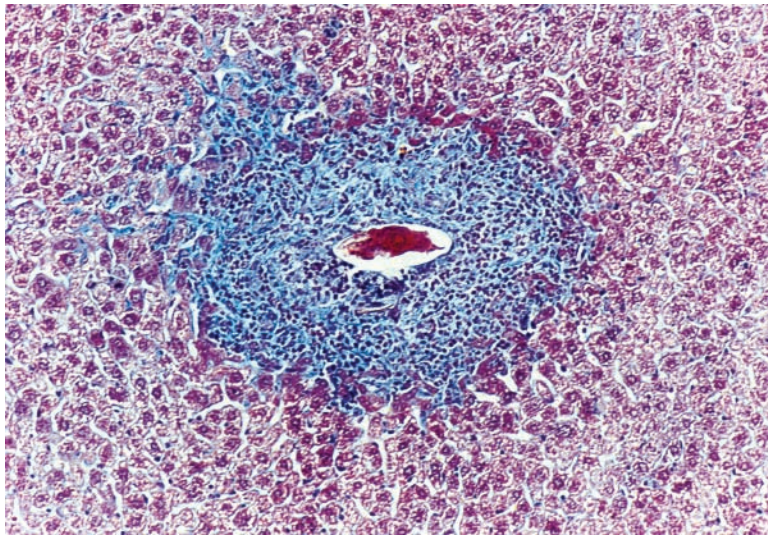
**Figure 2.** Fibrosis (stained in blue) surrounding an *S. mansoni* egg in the liver.

the Fc domain has been shown to slow in vivo clearance of TNFR-Fc fusion proteins. Now that this novel regulatory role for IL-13Rα2 has been identified, it will be important to address the mechanism by which this receptor is differentially modulating the levels of circulatory or tissue IL-13.

*Potential Role for IL-13Rα2 in Managing IL-13–induced Fibrosis.* Chiaramonte et al. (18) have followed up studies on IL-4 and IL-13 receptor expression during schistosome infection by assessing the responses of IL-13Rα2$^{-/-}$ mice to *Schistosoma mansoni* infection. Murine schistosome infections permit studies on many of the pathogenic processes that occur in human disease, including hepatic fibrosis and granuloma formation (Fig. 2) in response to CD4$^+$ T cells and type 2 cytokines (23). Previous studies by our laboratories, in which we infected IL-4$^{-/-}$, IL-13$^{-/-}$, and IL-4/IL-13$^{-/-}$ mice with *S. mansoni*, have clearly demonstrated that in the absence of either IL-4 or IL-13 the reciprocal cytokine is able to compensate for the other, generating almost all of the pathology observed after infection (24). Most importantly, however, only in the absence of IL-13 was hepatic fibrosis severely impaired. Similar findings using an IL-13 antagonist have also been reported (25). Chiaramonte et al. (18) demonstrate a complementary result, whereby infection of IL-13Rα2$^{-/-}$ mice with *S. mansoni* led to markedly elevated hepatic fibrosis when compared with infected wild-type animals. Their data also suggest that IL-13 induces IL-13Rα2 expression, suggesting the presence of a feedback mechanism to prevent excessive IL-13–induced fibrosis. Importantly, Chiaramonte et al. (18) did not find differences in a broad number of other pathological features associated with murine schistosome infection. Thus, these data infer a novel and specific role for IL-13Rα2 in suppressing IL-13–induced fibrosis caused by schistosome infection. Previous studies have shown that IL-13 may mediate fibrosis through at least two distinct pathways, acting directly on fibroblasts (Fig. 3) or by regulating other profibrotic factors (26). It will be interesting to determine, using models such as bleomycin–induced pulmonary
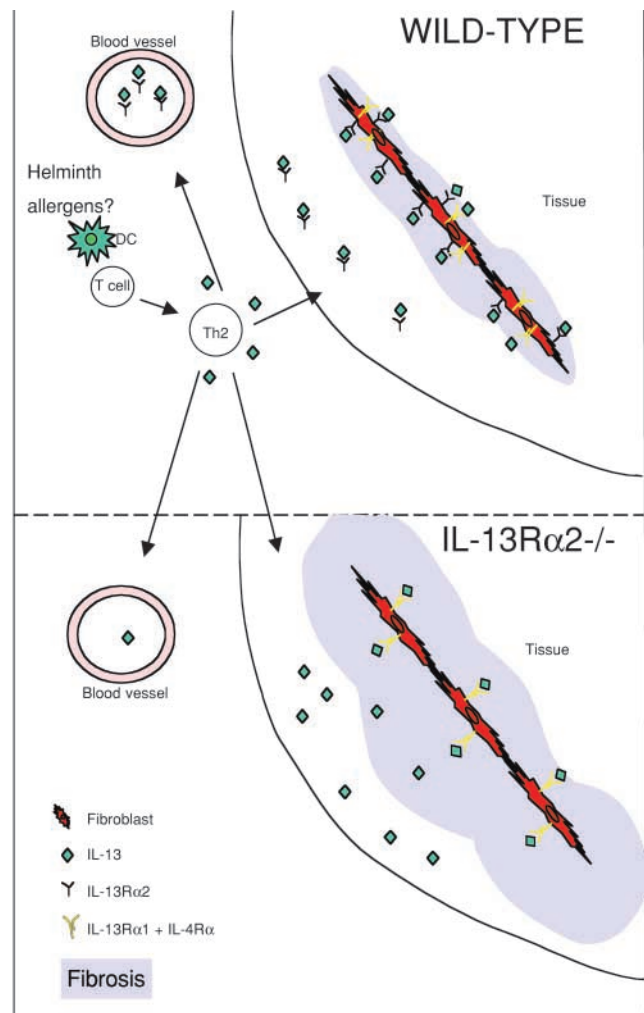


**Figure 3.** Schematic representation of IL-13Rα2 acting as a decoy receptor to attenuate IL-13–induced fibrosis.

fibrosis, the relative contribution of such pathways to the fibrosis reported in the IL–13Rα2$^{-/-}$ mice. Furthermore, Th2 cells play a central role in regulating the clinical manifestations of allergic disease and mouse models of allergic airways disease have been used to provide insights into these processes. Given the results obtained from the analysis of IL–13Rα2$^{-/-}$ mice infected with *S. mansoni*, it will be important to evaluate the potential role played by IL–13Rα2 in pulmonary allergic disease, particularly in the context of mucus production and fibrosis.

*Therapeutic Implications.* Soluble forms of many of the Th2 cytokine receptors have been identified in serum or urine, but their functional importance remains unclear. It has been suggested that the soluble receptors may act as antagonists of cytokine function and thereby limit the extent of ligand-induced activation. However, in some instances, for example IL–6Rα, soluble receptors are in fact agonists (27). Indeed, experiments in which the administration of soluble IL–13Rα1 was found to up-regulate the expression of IgM, IgG2a, and IgG2b from germinal center B cells may also suggest that this IL–13R subunit might act as an agonist (28). By contrast, IL–13Rα2 appears to have evolved to specifically inhibit the IL–13–mediated functions, though in the present schistosome infection study only an affect on fibrosis has been described. Blocking of cytokine functions, either using engineered ligands, receptors, or specific antibodies, is an attractive therapeutic strategy. IL–13 expression correlates strongly with the occurrence of allergic asthma and atopy and the associated expression of IgE (29). Recent studies using mouse models of experimental airway hypersensitivity have also demonstrated that IL–13 plays a central role in these responses, independent of IgE and eosinophilia (1, 2). Thus, inhibiting IL–13 responses may have tangible clinical benefits. To this end, a number of IL–13 antagonists have been described. Due to IL–4Rα being part of both the IL–4R complex and the IL–13R complex, mutant IL–4 analogs that act as competitive antagonists of IL–4 also compete with IL–13 for interaction with the IL–4Rα. A mouse IL–4 mutant protein with amino acid substitutions of Q116D and Y119D forms unproductive complexes with IL–4Rα and is an in vitro antagonist of IL–4 and IL–13 (30). Similarly, a human IL–4 homologue with a mutation of Y124D competes with both IL–4 and IL–13 and antagonizes B cell responses (31). In addition, antibody to IL–4Rα inhibits the action of both IL–4 and IL–13 (32). A more comprehensive understanding of the roles of the different IL–13 receptor chains in vivo, as indicated by the studies in this issue, will complement the ongoing search for IL–13 antagonists. To date, a recombinant soluble IL–13Rα2-Fc fusion protein has proven highly effective in inhibiting IL–13–induced responses (1, 2, 5, 15, 25) and a high affinity IL–13 cytokine trap, bringing together the IL–4Rα and IL–13Rα1, has also been reported (33).

The reasons for inappropriate Th1 or Th2 responses are complex but involve dysregulation of mechanisms that normally control cytokine levels. In the absence of these regulatory processes life-threatening disease pathology may arise. A number of regulatory processes, including decoy receptors (e.g., IL–1 type II receptor), have been described that limit Th1 proinflammatory cytokines. It is now evident that decoy receptors may also limit Th2 responses and thus provide an important mechanism for the regulation of serum and tissue levels of Th2 cytokines. IL–13 decoy receptors may function to protect against uncontrolled Th2 inflammatory responses and thereby help in maintaining the balance between Th1 and Th2 pathology.

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