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IL-13 EFFECTOR FUNCTIONS*

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■ **Abstract** IL-13 was first recognized for its effects on B cells and monocytes, where it upregulated class II expression, promoted IgE class switching and inhibited inflammatory cytokine production. It was also thought to be functionally redundant with IL-4. However, studies conducted with knockout mice, neutralizing antibodies, and novel antagonists demonstrate that IL-13 possesses several unique effector functions that distinguish it from IL-4. Resistance to most gastrointestinal nematodes is mediated by type-2 cytokine responses, in which IL-13 plays a dominant role. By regulating cell-mediated immunity, IL-13 modulates resistance to intracellular organisms including *Leishmania major*, *Leishmania mexicana*, and *Listeria monocytogenes*. In the lung, IL-13 is the central mediator of allergic asthma, where it regulates eosinophilic inflammation, mucus secretion, and airway hyperresponsiveness. Manipulation of IL-13 effector function may also prove useful in the treatment of some cancers like B-cell chronic lymphocytic leukemia and Hodgkin's disease, where IL-13 modulates apoptosis or tumor cell growth. IL-13 can also inhibit tumor immunosurveillance. As such, inhibitors of IL-13 might be effective as cancer immunotherapeutics by boosting type-1-associated anti-tumor defenses. Finally, IL-13 was revealed as a potent mediator of tissue fibrosis in both schistosomiasis and asthma, which indicates that it is a key regulator of the extracellular matrix. The mechanisms that regulate IL-13 production and/or function have also been investigated, and IL-4, IL-12, IL-18, IFN-γ, IL-10, TGF-β, TNF-α, and the IL-4/IL-13 receptor complex play important roles. This review highlights the effector functions of IL-13 and describes multiple pathways for modulating its activity in vivo.

INTRODUCTION

IL-13 was originally described as a T cell–derived cytokine that inhibits inflammatory cytokine production (1, 2, 3). Though this original description remains accurate, the known effector functions of IL-13 have expanded dramatically over the past few years. This increase in knowledge is primarily attributable to the

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development of several unique experimental animal models that either promote or block the activity of IL-13. Early studies comparing IL-4-, IL-4R-, and Stat6-deficient mice were the first to suggest a nonredundant role for IL-13 in host immunity (4–8). Since then, at least two IL-13 transgenic mice have been developed that overexpress IL-13 in the lung (9) or in lymphoid tissues (10). Two distinct IL-13-deficient animals have also been generated. One has a disruption in exon 1 (11) and the second a neocassette inserted into exon 3 (12). Both knockout animals were instrumental in demonstrating nonredundant roles for IL-13. Mice simultaneously deficient in IL-4 and IL-13 were also valuable tools and highlighted the cooperative and distinct functional activities of IL-4 and IL-13 (13). In addition to transgenic and knockout mice, novel IL-13 antagonists and neutralizing antibodies have also been generated and offer the advantage of blocking IL-13 at various time points and in other transgenic mice (14–16). Moreover, the utility of IL-13-deficient mice alone to study IL-13 effector function may be limited because the mice appear to manifest a partial defect in the closely linked IL-4 gene (17). This must be taken into consideration when comparing findings generated from knockout and IL-13-blocking studies and may explain some of the published functional discrepancies.

The list of important effector functions mediated by IL-13 continues to grow and includes a diverse array of biological activities including regulation of gastrointestinal parasite expulsion, airway hyperresponsiveness (AHR), allergic inflammation, tissue eosinophilia, mastocytosis, IgE Ab production, goblet cell hyperplasia, tumor cell growth, intracellular parasitism, tissue remodeling, and fibrosis. Although IL-4 and IL-13 are functionally related, it is surprising to note in many situations IL-13 appears to play a more important role than IL-4. The general availability of both ligands and the particular receptor combinations expressed on responding cells likely dictates the overall importance of IL-4 versus IL-13 in specific disease settings. This review focuses on the effector functions of IL-13, revealed primarily through knockout, blocking, and transgenic mouse studies. The various mechanisms that regulate the production and/or effector activities of IL-13 are also discussed. The findings generated over the past few years illustrate a complex and pleiotropic nature for IL-13 in host immunity. More importantly, they emphasize that IL-13 is an important target for therapeutic intervention.

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THE CENTRAL ROLE OF IL-13 IN DISEASE SUSCEPTIBILITY AND RESISTANCE

Resistance to Gastrointestinal Nematodes

Helminth parasites induce strong Th2 responses that contribute to the mast cell, eosinophil, giant cell, IgE/IgA, and mucus responses, which are hallmarks of these infections. For intestinal helminths in particular it is clear that elements of the type 2 response are critical for host resistance to infection (18). The mechanisms involved have been investigated intensively and experimental studies with *Nippostrongylus*

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brasiliensis were the first to reveal a unique and nonredundant role for IL-13 in host immunity (8, 11). Since then, several worms have been studied in detail in this regard: *Trichuris muris*, a natural parasite of the mouse and closely related to human whipworm, *Heligomosoides polygyrus*, and *Trichinella spiralis*, as well as *N. brasiliensis*, the rat hookworm.

In *N. brasiliensis* infection, parasites infect mice through the skin, migrate to the lungs, are coughed up, swallowed, develop into adults in the gut lumen, produce eggs that are excreted in the feces, and are themselves expelled approximately 10 days postinfection (18). Although studies show the expulsion mechanism requires a $CD4^+$ Th2 cell response (19), IL-4 itself is not critical because anti-IL-4 mAb-treated and IL-$4^{-/-}$ mice are as resistant to infection as WT animals (20, 21). As such, these studies were the first to suggest that another Th2 cell-derived mediator might be more important for worm expulsion. IL-13 was a likely candidate because IL-4Rα-deficient, Stat6-deficient, and IL-4/IL-13-deficient mice are all much more susceptible than animals deficient in IL-4 alone (7, 8, 13). Studies conducted with a soluble IL-13 antagonist (8) and in IL-13-deficient mice (11) confirmed the critical and nonredundant role of IL-13 in immunity to *N. brasiliensis*. Thus, although exogenous rIL-4 (22) and rIL-13 (7, 11) are both capable of stimulating resistance in susceptible hosts, the blocking and knockout studies conducted in resistant animals suggested IL-13 is the more important endogenous mediator of resistance. Moreover, the fact that IL-13 is capable of stimulating parasite expulsion even in immunodeficient RAG2$^{-/-}$ mice (7) suggests IL-13 mediates parasite expulsion by directly activating a yet undefined nonlymphoid cell within the gut. In support of this conclusion, recent evidence suggests expression of IL-4Rα by non–bone marrow–derived gastrointestinal cells is sufficient for parasite elimination (23).

In contrast to *N. brasiliensis* infection, where IL-13 clearly plays a superior role to IL-4, both cytokines appear to be necessary for optimal immunity to *T. muris*. *T. muris* and *H. polygyrus* are both transmitted by the oral-fecal route independently of an intermediate host, and, in some strains of mice, they cause chronic infections. In the case of *T. muris*, susceptibility depends on the mouse strain, where some animals reject the parasite shortly after exposure and others develop long-lived infections (24). In this system, resistant mice express type 2 responses, susceptible mice mount type 1 responses, and IL-12 can induce a switch from a protective type 2 to an infection-permissive type 1 response. Similarly, in normally susceptible strains, in vivo depletion of IFN-γ or IL-12 allows the expansion of a type-2 response and effective clearance of infection (24). In contrast to *T. muris*, most strains of mice are susceptible to a primary *H. polygyrus* infection, but following drug clearance animals exhibit a strong type 2 response and are highly resistant to secondary infections. Similar to *N. brasiliensis* infection, $CD4^+$ T cells are required for the induction and/or expression of immunity to both *H. polygyrus* and *T. muris* (24). Exogenous IL-4 can cure primary infections with *T. muris* and *H. polygyrus*, anti-IL-4R mAb blocks resistance to both, and IL-$4^{-/-}$ mice are susceptible to a challenge infection with *H. polygyrus* or a primary infection with *T. muris* (24, 25). The relative role of IL-4, however, depends on

the background of the mouse because C57BL/6 IL-4 KO mice develop chronic *T. muris* infections, whereas some BALB/c IL-4 KO mice clear their infections (26–28). This latter finding suggested an IL-4-independent role for IL-13 in resistance, which was confirmed by treating BALB/c IL-4-deficient mice with an IL-13 antagonist (27). A recent study suggested differences in IFN-γ production in C57BL/6 versus BALB/c mice likely dictate the relative importance of IL-13 and/or IL-4 in *T. muris* immunity (29). Indeed, chronic infections are also established in IL-13-deficient mice despite the fact that they develop relatively normal IL-4 responses (26), which thus further emphasizes the cooperative and additive roles of IL-4 and IL-13 in immunity to *T. muris*.

Similar to what is observed during *T. muris* and *N. brasiliensis* infection, IFN-γ also antagonizes the actions of IL-4 and IL-13 in *T. spiralis* infection, effectively suppressing parasite expulsion. In contrast to *T. muris* infection, however, expulsion of *T. spiralis* proceeds normally in the absence of IL-4 or IL-13. Thus, expulsion is prevented only in the combined absence of both cytokines (30). Spontaneous *T. spiralis* expulsion also requires expression of IL-4Rα and Stat6 (30, 31). As such, many observations made with *T. spiralis* closely resemble findings with *N. brasiliensis*, except IL-13 is clearly more important than IL-4 for expulsion of the latter. In contrast to *N. brasiliensis*, however, where IL-13 appears to have direct effects on the gut, *T. spiralis* expulsion appears to be mediated indirectly by IL-13, IL-4Rα, and Stat6 by enhancing IL-13 and IL-4 and suppressing IFN-γ production; this, in turn, enhances the intestinal mast cell response required for *T. spiralis* expulsion (30).

Extrapolation of the findings from these various experimental systems to state that resistance to intestinal nematodes requires Th2-mediated responses is supported by recent studies that provide new insight as to how IL-4 and IL-13 actually function to mediate protection. In uninfected mice, IL-4 has dramatic effects on intestinal physiology causing increased mucosal permeability and reduced sodium-linked glucose absorption (18, 32). Muscle hypercontractility and goblet-cell hyperplasia are also regulated in the gut by IL-4 and IL-13 and are attenuated by IL-12 treatment, possibly implicating them in the resistance mechanism (31–35). For the most part, these protective responses appear to be T cell and mast cell dependent (18). Their net effect is to trap parasites in mucus within the gut lumen, to increase intestinal fluid content, and to increase contractility, all of which facilitate expulsion of parasites via a "weep and sweep" mechanism (18, 32). Recent studies indicate that many of these properties are shared by IL-13 (36). Indeed, IL-13 has a greater effect on intestinal smooth muscle contractility than IL-4 (37). The hypercontractility induced by IL-13 is mediated by direct effects on the smooth muscle cell as well as by an action on enteric nerves.

Regulation of Intracellular Parasitism

Although control of many extracellular parasitic infections requires a Th2-polarized immune response, resistance to most intracellular parasites requires a strong cell-mediated response, where $CD4^+$ Th1 effector cells play a prominent role. The

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immune response to Leishmania parasites is no exception and is arguably one of the most well-studied systems in the field of immunoparasitology. Infection with *Leishmania major* in susceptible BALB/c mice results in a Th2-dominant immune response, progressive disease, and eventual death (38). Most other strains of mice develop strong Th1 responses, and consequently, they kill the majority of parasites within the inoculation site and fail to develop significant lesions. Thus, low-grade infection without significant disease is the most common outcome following infection with *L. major* (39). Early studies suggested IL-4 was likely the key factor influencing resistance versus susceptibility (38); however, a plethora of studies now indicate several host genes are involved (40–42), and the parasite substrain and/or Leishmania species also play a significant role (43, 44).

Localized cutaneous leishmaniasis lesions express high levels of IL-13 (45), and over 50% of patients with visceral leishmaniasis have detectable levels of IL-13 in their serum, whereas many fewer have a detectable IL-4 response (46). These observations provided, from infected humans, evidence of a possible regulatory role for IL-13 in disease progression, which was recently investigated in a series of experimental studies where *L. major* infection was compared in BALB/c IL-4-, IL-4Rα-, Stat6-, and IL-13-deficient mice (43, 44, 47–50). In one study, genetically pure BALB/c IL-4$^{-/-}$ and IL-4R$\alpha^{-/-}$ mice were fully susceptible to LV39, whereas IL-4$^{-/-}$ mice were partially resistant and IL-4R$\alpha^{-/-}$ mice were highly resistant to the IR173 substrain (43). This finding provided the first experimental evidence linking IL-13 with nonhealing infections in BALB/c mice. Subsequent studies conducted in BALB/c IL-13- and IL-4/IL-13-deficient mice confirmed the role of IL-13, which is important because they showed that there is an additive protective effect of deleting IL-4 and IL-13 (49). However, it remains unclear how ubiquitous the contribution of IL-13 will be because growth of the LV39 substrain was little affected by IL-4Rα deficiency (43). Moreover, studies conducted with a second cutaneous leishmaniasis strain, *L. mexicana*, demonstrated no role for IL-13 in susceptibility (44), although this finding is disputed in a more recent study (51). These findings suggest other susceptibility factors, such as IL-10 and TGF-beta (39, 52), may also play significant roles during Leishmania infection, as suggested by genetic linkage studies.

In contrast to the findings of Noben-Trauth et al. (43), a protective role for IL-13 was postulated in a second study comparing *L. major* infection in BALB/c IL-4$^{-/-}$ and IL-4R$\alpha^{-/-}$ mice (48). However, in this study, the authors' interesting findings were revealed in the chronic phase of infection, when additional factors are believed to be needed for the complete healing and elimination of parasites. In these studies, IL-4R$\alpha^{-/-}$, but not IL-4$^{-/-}$, mice infected with the LV39 strain showed signs of progressive and disseminating lethal disease approximately 80 days postinfection. Prior to this point in time, however, both strains of mice appeared to be fully resistant and effectively restricted parasite growth. The different outcomes displayed between IL-4$^{-/-}$ and IL-4R$\alpha^{-/-}$ mice suggest that IL-13-mediated effector functions are involved in controlling dissemination of the parasite in chronic leishmaniasis. It remains unclear, however, why IL-13 displays an exacerbative role in

the early phases of some leishmanial infections (43, 51) and protective activity in the chronic phase (48), but it will likely prove an exciting area of future research. It is interesting that a similar protective role for IL-13 was also reported in mice infected with the intracellular pathogen, *Listeria monocytogenes* (53). In this case, rIL-13 increased IL-12 p40 and p70 production by infected bone marrow–derived macrophages, implicating IL-13 in the initiation and/or maintenance of protective cell-mediated immunity.

Inflammatory Diseases of the Lung

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One of the areas where the in vivo biological activity of IL-13 has been investigated intensively is the lung; many important findings have come out of this research in the past few years alone. Several distinct disease models have been studied in this regard including models of pathogen-induced pulmonary inflammation (54, 55), asthma (9, 56, 57), anaphylaxis (58), hyperoxic acute lung injury (59), emphysema, and chronic obstructive pulmonary disease (COPD) (60). When viewed together, it is clear that IL-13 plays a critical and nonredundant role in the pathophysiology of the lung.

One of the first studies to report pulmonary expression of IL-13 was an experimental model of Th2-mediated granulomatous disease (61). In this model, eggs of the helminth parasite *Schistosoma mansoni* are injected intravenously into naïve or egg-sensitized mice, and the animals mount a vigorous granulomatous response in the lung. Consistent with many helminthic diseases, Th2-type cytokines dominate the response, and studies conducted with exogenous IL-12 showed the Th2-type response is critical for normal egg-induced lesion formation (61). Since then, at least three separate groups using different approaches have attempted to dissect the individual contributions of IL-4 and IL-13 in pulmonary granuloma formation (13, 16, 54). In one study, sIL-13Rα2-Fc treatment reduced peak granuloma size in both naïve and egg-sensitized mice by $\sim$50% (54). However, when similar experiments were conducted in IL-4-deficient mice, granuloma formation and tissue eosinophilia were almost completely ablated, which demonstrated that IL-4 and IL-13 play additive roles in pulmonary lesion formation. Similar conclusions were generated in studies using IL-4-, IL-13-, and IL-4/IL-13-deficient mice (13) or anti-IL-13 mAbs (16).

The individual roles of IL-13 and IL-4 in the pathogenesis of asthma have also been the subject of several research programs in the past few years. Previous studies showed that although IL-4 drives Th2 cell development, it does not appear to be necessary for the expression of allergic asthma, which suggests a more important role for other Th2 family members (62). To elucidate the various effector functions of IL-13, Zhu and colleagues engineered a mouse that specifically overexpresses IL-13 in the lung (9). These mice, in contrast to their transgene negative littermates, developed several characteristics of asthma including pulmonary eosinophilia, airway epithelial cell hyperplasia, mucus cell metaplasia, subepithelial fibrosis, Charcot-Leyden-like crystals, airways obstruction, and nonspecific

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airways hyperresponsiveness to cholinergic stimulation. IL-13 blockade inhibited many of the same characteristics in allergen-immunized wild-type mice, which is important because it reveals for the first time the critical and nonredundant role of IL-13 in allergen-induced AHR (56, 57). Thus, although exogenous IL-4 and IL-13 are both capable of inducing an asthma-like phenotype (56, 57, 63), as reported with some of the gastrointestinal parasites (8, 11), the effector activity IL-13 appears to be superior to that of IL-4.

Given the overall importance of these findings, the mechanism underlying the IL-13-dependent expression of AHR has been a major research focus. Because IL-4 and IL-13 both utilize the IL-4Rα chain for signaling, it was probably not unexpected that the activity of IL-13, at least in these acute asthma models, is abrogated in IL-4Rα- and Stat6-deficient animals (57, 64–67). One of the more important early findings demonstrated that exogenous IL-13 can also induce AHR in the absence of T and B cells (57). This finding was one of the first to suggest a direct role for IL-13, which has been substantiated in several other studies (68–71). Eosinophils have also been implicated as primary effector cells in asthma and asthmatic AHR; however, allergen-induced pulmonary eosinophilia was not significantly affected in one of the studies using sIL-13Rα2-Fc treatment (56), potentially lessening their overall importance to AHR. Antigen-specific IgE was also unchanged in IL-13 antagonist-treated mice (56), indicating that AHR is not dependent on IgE production; these findings are consistent with studies conducted in IgE-deficient mice (72).

Subsequent AHR studies conducted in IL-13-deficient mice have suggested that IL-13 might instead play more of an additive role with IL-4 (73); however, these findings remain somewhat controversial (74). It may also prove inappropriate to directly compare results generated with IL-13 antagonists and IL-13-deficient mice because the latter animals may display a partial defect in the closely linked IL-4 gene (17). Nevertheless, the findings from IL-13-deficient mice have confirmed the importance of the IL-13-, IL-4Rα-, Stat6-dependent pathway in the induction of AHR. In one study, AHR failed to develop in Ovalbumin (OVA)-sensitized and challenged IL-13$^{-/-}$ mice, despite the presence of a strong Th2-biased pulmonary eosinophil response (74). Administration of rIL-13, however, completely restored AHR in the knockout animals. Moreover, OVA-specific Th2 cells derived from TCR-transgenic IL-13$^{-/-}$ mice failed to induce AHR in recipient SCID mice even though they produced high levels of IL-4 and IL-5 and had a significant eosinophilic infiltrate. These studies suggested that IL-13 was, by itself, necessary and sufficient to induce AHR. Nevertheless, a second study using IL-13$^{-/-}$ mice showed that it is possible for AHR and pulmonary eosinophilia to develop in the absence of IL-13 (73). Here, AHR was reduced in IL-13$^{-/-}$ mice only when they were treated with either anti-IL-4 or anti-IL-5 mAbs, which suggests additive roles for IL-13, IL-4, IL-5, and tissue eosinophilia in the development of AHR.

Consistent with findings that suggest a direct role for IL-13 in AHR, a recent study showed that IL-13-induced AHR and mucus secretion can occur independently of IL-5 and/or the eosinophil chemoattractant eotaxin (67). It is important

to note this study also showed AHR-inducing activity for IL-13 in the early preinflammatory phase, which is characterized by an absence of inflammation (eosinophilia) and mucus hypersecretion. Thus, although IL-13-induced recruitment of eosinophils to lung requires IL-5 and eotaxin (75), the eosinophil regulatory circuit does not appear to be necessary for the development of AHR or mucus hypersecretion when IL-13 is abundant. Nevertheless, subsequent studies have suggested that IL-5 and eotaxin may both be required to maintain IL-13 production in $CD4^+$ Th2 cells (76). Indeed, the ability of Th2 cells to produce IL-13 was significantly impaired in mice deficient in IL-5/eotaxin. However, this T cell IL-13 defect was overcome when eosinophils were transferred to the double knockout mice. Thus, the IL-5, eotaxin, eosinophil regulatory circuit is not necessarily a dispensable effector pathway in allergic disease because it appears to play a central role in regulating production of the key effector cytokine, IL-13.

It is surprising that, although many features of allergic airway disease are IL-4Rα chain- and Stat6-dependent, at least two recent papers have shown that IL-13 may also function in the absence of these downstream mediators (77, 78), which possibly suggests a novel pathway for IL-13 signaling. In one study, IL-13-sufficient and IL-13-deficient OVA-specific T cells were adoptively transferred to naïve BALB/c WT and IL-4R$\alpha^{-/-}$ mice concurrently with OVA delivery to the airways (77). The IL-13-expressing T cells were found unexpectedly to induce several features of asthma independently of the IL-4Rα chain. The IL-$13^{+/+}$ cells were, however, completely ineffective in Stat6-deficient mice. Together, these observations suggest a novel IL-13 receptor signaling system must exist to modulate allergic disease, which does not require the IL-4Rα chain but utilizes the Stat6-signaling cascade. This is consistent with a recent study that suggested Stat6-deficient mice are protected from all pulmonary effects of IL-13. However, reconstitution of Stat6 only in epithelial cells was sufficient for IL-13-induced AHR and mucus production (79). These findings argued for direct IL-13/Stat6-induced effects on epithelial cells. Nevertheless, a separate study of chronic fungal asthma suggested that a Stat6-independent but IL-13-dependent pathway might also exist (78). Thus, though nearly every published study points to IL-13 as a key effector cytokine in asthma, the downstream events and cellular targets of IL-13 remain somewhat unclear and will certainly be an exciting research focus in the coming years.

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Cancer

Another important area of research is in the field of cancer where depending on the tumor cell type in question, targeting IL-13 or IL-13 receptors may either inhibit or promote tumor cell growth. Early in vivo studies showed potent antitumor activity for both IL-4 and IL-13 in mice. IL-4 inhibited the proliferation of several human cancer cell lines, including various hematologic malignancies as well as non–small cell lung cancer, colon cancer, head and neck carcinomas, and glioblastomas (80). Similar antiproliferative effects on human breast cancer cells, renal cell carcinoma, and B-lineage acute lymphoblastic leukemia were also shown for IL-13 (81–84). In one study, the growth inhibition mediated by IL-13 was completely reversible

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by anti-IL-4 receptor antibody treatment (84), which demonstrated that a classical type II IL-4 receptor and a Stat6-signaling cascade were involved. In another study, mice injected with transfected P815 mastocytoma cells secreting large amounts of IL-13 rejected their tumors and developed systemic specific antitumor immunity leading to long-lasting specific antitumor protection. In vivo, overexpression of the IL-13Rα2 chain in the tumor inhibits the tumorigenicity of some breast and pancreatic cancers in immunodeficient mice (85). In each case, activation of specific and/or nonspecific antitumor defenses by IL-13 or IL-13Rα2 was postulated as the primary explanation for the observed antitumor response (86).

Nevertheless, subversion of host antitumor defenses has also been demonstrated for IL-13. Type 1 T cell–mediated host defenses are widely believed to mediate optimal tumor rejection in vivo. Therefore, deviation toward a more dominant Th2-type response has been postulated as a mechanism that might block tumor rejection and/or promote tumor recurrence (87). In support of this hypothesis, three recent studies using transplantable tumor cell lines demonstrated that Stat6, IL-4, and IL-13 were capable of inhibiting tumor rejection (88–90). In contrast to wild-type mice that showed progressive growth of their tumors, Stat6-deficient mice were highly resistant and spontaneously rejected the transplanted tumor cells. Enhancement of tumor-specific IFN-γ production and CTL activity in the absence of Stat6 was proposed as the primary explanation for the potent antitumor activity. In one of the studies, the authors were investigating the mechanisms regulating tumor immunosurveillance (88). In this model, tumors spontaneously regress after initial growth; however, within 20 to 40 days, they recur. Here, the mechanism of tumor regression is mediated by $CD8^+$ cytotoxic T lymphocytes specific for a model tumor antigen HIV gp160. These authors showed that IL-4Rα- and Stat6-, but not IL-4-deficient, animals were highly resistant to tumor recurrence, which implicated IL-13 as the primary mediator. When susceptible WT or IL-4-deficient mice were treated with IL-13 inhibitor, tumor recurrence was almost completely blocked (88). It is interesting that loss of natural killer T cells (NKT cells) in CD1-deficient mice resulted in decreased IL-13 production and resistance to recurrence. Thus, IL-13, produced in part by NKT cells, appears to antagonize tumor immunosurveillance. As such, these findings suggest IL-13 inhibitors or novel IL-13 antagonists may prove highly effective as cancer immunotherapeutics.

In addition to boosting type-1-associated antitumor defenses, in some situations IL-13 inhibitors may also block tumor cell growth more directly. Such is the case with B chronic lymphocytic leukemia (B-CLL) and Hodgkin's disease, where IL-13 either blocks apoptosis or promotes tumor cell proliferation (91, 92). In the case of B-CLL, IL-13 does not exhibit direct growth factor activity but instead protects B-CLL cells from in vitro spontaneous apoptosis (2, 91, 93). Thus, IL-13 may be an important factor in the pathogenesis of CLL by preventing the death of neoplastic cells. In Hodgkin's disease, a condition that mostly affects young adults, tumors are typically detected in lymph nodes in the neck and chest, with eventual spread throughout the lymphatic system. The cancer is characterized by the presence of Hodgkin/Reed-Sternberg cells (H/RS), which are large multinucleated cells that rarely occur throughout the lymph tissue. In a large majority of cases, the

malignant cell population arises from B cells. Several Hodgkin's disease cell lines overexpress IL-13 and IL-13 receptors. Lymph node tissues taken from Hodgkin's disease patients also exhibit high levels of the cytokine (92, 94–96). Constitutive activation of Stat6 was also reported in Hodgkin's lymphoma cell lines (97). More importantly, however, neutralizing anti-IL-13 mAbs or IL-13 antagonists inhibited H/RS cell proliferation in a dose-dependent manner (92, 96). Increased apoptosis was also observed following IL-13 blockade. Thus, the available evidence suggests IL-13 stimulates the proliferation of H/RS cells in an autocrine fashion (92, 98). As such, neutralization of IL-13 may represent an attractive and highly effective treatment for Hodgkin's lymphoma and other B cell–associated cancers by inhibiting tumor cell growth and simultaneously enhancing antitumor defenses (88–90).

Given that many tumor cell types overexpress IL-4/IL-13 receptors, the receptors themselves have also been exploited as possible targets for cancer therapy. By linking human IL-13 with a mutated form of Pseudomonas exotoxin (99), Puri and colleagues have developed a novel fusion protein that is highly cytotoxic to several IL-13 receptor-positive tumor cells, including glial, renal, AIDS-associated Kaposi's tumors, squamous cell carcinoma of head and neck and prostate cancer cells, as well as several human epithelial carcinomas such as adenocarcinoma of the stomach, colon, and skin (14, 100–105). In this system, the toxin kills tumor cells but only after they internalize the ligand-receptor complex. The cytotoxic action of the IL-13-toxin is blocked when excess human IL-13 is included, which further confirms the high specificity of the reaction. With some tumor cell types, the IL-13-toxin appears to be more effective than a similarly engineered IL-4 chimeric protein because the tumors preferentially express high levels of IL-13Rα2 (82, 106–108). A mutation was also recently engineered in the IL-13 portion of the fusion protein to alter its interaction with the IL-13 receptor, which decreased its toxicity on normal tissues and simultaneously enhanced its antitumor activity (109, 110). Thus, targeting the IL-13/IL-13 receptor system may prove highly effective in the treatment of several malignancies. Nevertheless, given that IL-13 can exhibit both pro- and antitumorigenic activity, the exact role of IL-13 must be carefully dissected in each case so that the most appropriate IL-13-based strategy is implemented.

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Tissue Remodeling and Fibrosis

In the helminth infection, *Schistosoma mansoni*, adult parasites reside in the mesenteric veins where they lay hundreds of eggs per day. Some of the eggs become entrapped in the microvasculature of the liver, and once there, they induce a granulomatous response (111). Subsequently, fibrosis and portal hypertension may develop, which is the primary cause of morbidity in infected individuals and in some cases may be lethal (112). Consequently, much of the symptomatology of schistosomiasis is attributed to the egg-induced inflammatory response and associated fibrotic liver pathology.

$CD4^+$ Th cells are essential for granuloma formation, and early studies examining the respective roles of Th1- and Th2-associated cytokines showed that the granulomatous response evolves from early Th1 to sustained and dominant

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Th2-type cytokine response (113, 114). The importance of Th2 cells to this pathologic process was shown by experiments in which mice vaccinated with egg antigen plus IL-12, to induce an egg-specific Th1 response upon subsequent infection, developed smaller granulomas and less severe fibrosis than did nonvaccinated infected controls (61, 115). Decreased fibrosis was associated with a diminished IL-4/IL-13 response and increased type-1 cytokine production. Although Th2-mediated pathology is ultimately detrimental to the host, it is also clear that granulomas serve an important host-protective function during infection. In chronically infected hosts, schistosome eggs provide a continuous antigenic stimulus for the immune response. If these antigens are not sequestered or neutralized effectively, they may damage host tissues, the liver being particularly sensitive. In support of this conclusion, T cell–deprived, nude, SCID, egg-tolerized, and some IL-$4^{-/-}$ and IL-$10^{-/-}$ mice die earlier than comparably infected, immunologically intact control mice because they are unable to satisfactorily mount a normal Th2-dominant response (116–119). Widespread microvesicular hepatic damage induced by toxic egg products contributes to the poorer survival of the infected immunosuppressed mice. Presumably, the chronic detrimental effects associated with egg granulomas (e.g., fibrosis and portal hypertension) represent a compromise solution for the host and parasite because the parasite will only survive when the host is effectively protected from these hepatotoxins. Nevertheless, although the Th2 response plays a host-protective role, persistent expression of these mediators will also scar the liver, which eventually contributes to the development of hepatosplenic disease. The Th2 response, therefore, represents a double-edged sword by exhibiting protective and host-damaging activities during acute and chronic infection, respectively.

It is surprising that early IL-4 ablation experiments and studies with IL-4-deficient mice failed to demonstrate a significant role for IL-4 in the development of fibrosis (111, 120). In contrast, granuloma size and fibrosis markedly decreased in Stat6- and IL-4R$\alpha^{-/-}$ animals (121, 122), implicating IL-13 (54). Microscopic, biochemical, and molecular techniques all indicated that IL-13, but not IL-4, plays the major role in the development of egg-induced fibrosis (123, 124). Earlier studies showed that perturbations in the Th1/Th2 cytokine balance can also significantly affect the extent of tissue fibrosis in *S. mansoni*–infected mice (115). However, the IL-13 blocking studies suggested the effects of IL-13 might be more direct. Similar conclusions were drawn from studies conducted in *S. mansoni*–infected IL-13 and IL-4/IL-13-deficient mice (125). Mortality was delayed significantly in infected IL-13-deficient animals, further highlighting the major contribution of IL-13 to the pathogenesis of schistosomiasis. In vitro studies showed that IL-13 is a potent activator of collagen production in fibroblasts (123). Thus, the effects of IL-13 on fibrosis may indeed be direct and not dependent upon induction of other profibrotic mediators or perturbations in the Th1/Th2 cytokine response. Studies conducted with IL-13 on normal human skin and keloid fibroblasts also suggested a direct role for IL-13 in collagen production (126). Additional studies are needed, however, to determine whether other mediators are involved, such as TGF-β, as suggested in a murine asthma model (127), and whether granuloma-derived fibroblasts exposed to IL-13 exhibit similar collagen-producing activity.

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Although activated fibroblasts are the primary producers of collagen, recent studies suggest macrophages and dendritic cells may be equally important mediators of IL-13-induced fibrosis (128) and Th2-mediated inflammation in general (129). Macrophages possess two cytokine-inducible enzymes, NOS-2 and arginase (Arg-1), which share L-arginine as a substrate. Modolell and colleagues showed that Th1-type cytokines activate NOS-2 in macrophages designated "classically activated," whereas the Th2-type cytokines IL-4 and IL-13 stimulate Arg-1 activity in macrophages termed alternatively activated (130). Similar observations were generated with dendritic cells (131). Arginase uses L-arginine as a substrate to make L-ornithine, which is converted to proline by ornithine-aminotransferase and to polyamines by ornithine decarboxylase. Proline is an essential amino acid involved in collagen production and, therefore, is necessary for the development of fibrosis. Fibrosis is inhibited in mice sensitized with egg antigens plus IL-12 (115), which appears to be owing to the induction of NOS-2 rather than arginase. NOS-2 uses arginine to make nitric oxide (NO) and citrulline. An intermediate product in this pathway, L-hydroxyarginine is also a potent inhibitor of arginase. Thus, in Th1-polarizing conditions, consumption of arginine by NOS-2 is increased, which blocks arginase, effectively reducing the amount of proline that is available for collagen synthesis (128). The IL-12 sensitization protocol is completely ineffective in NOS-2-deficient mice despite induction of a strong Th1 response (132). Here, competition for arginine by NOS-2 and production of the arginase inhibitor L-hydroxyarginine is eliminated, thus allowing for unobstructed arginase activity and a vigorous fibrotic response. These findings are particularly exciting because they provide a mechanistic explanation for the induction of fibrosis by IL-13 by showing a direct connection between the immune response (Th1 versus Th2), fibroblasts, and the arginine metabolic pathway in macrophages and dendritic cells (Figure 1).

The link between IL-13 and fibrosis revealed in the murine schistosomiasis model may also extend to other Th2-associated diseases. Indeed, tissue

Figure 1 IL-13 effector functions.Type-1 cytokines stimulate nitric oxide production in classically activated macrophages, whereas IL-13 produced by multiple cell types preferentially activates Arginase-1 and production of L-ornithine in alternatively activated cells. L-ornithine serves as substrate for ornithine-decarboxylase (ODC) and ornithine-amino transferase (OAT), which generate polyamines and proline, respectively. Proline is an essential amino acid used in collagen production. Fibroblasts are another significant target of IL-13 activity. IL-13 may act directly on fibroblasts or indirectly by stimulating and activating TGF-β production in macrophages. In addition, smooth muscle, mucus-producing cells, B cells, endothelium, and epithelium are also important target cells that ultimately regulate a wide-variety of IL-13-associated effector functions. The type-2 cytokine response also upregulates IL-13Rα2 expression (IL-13 decoy receptor), which dampens IL-13 effector activity. In contrast, the type-1 response appears to antagonize IL-13Rα2 expression in vivo, which may increase IL-13 effector activity when IL-13 levels are low or when mixed Th1/Th2 responses prevail.

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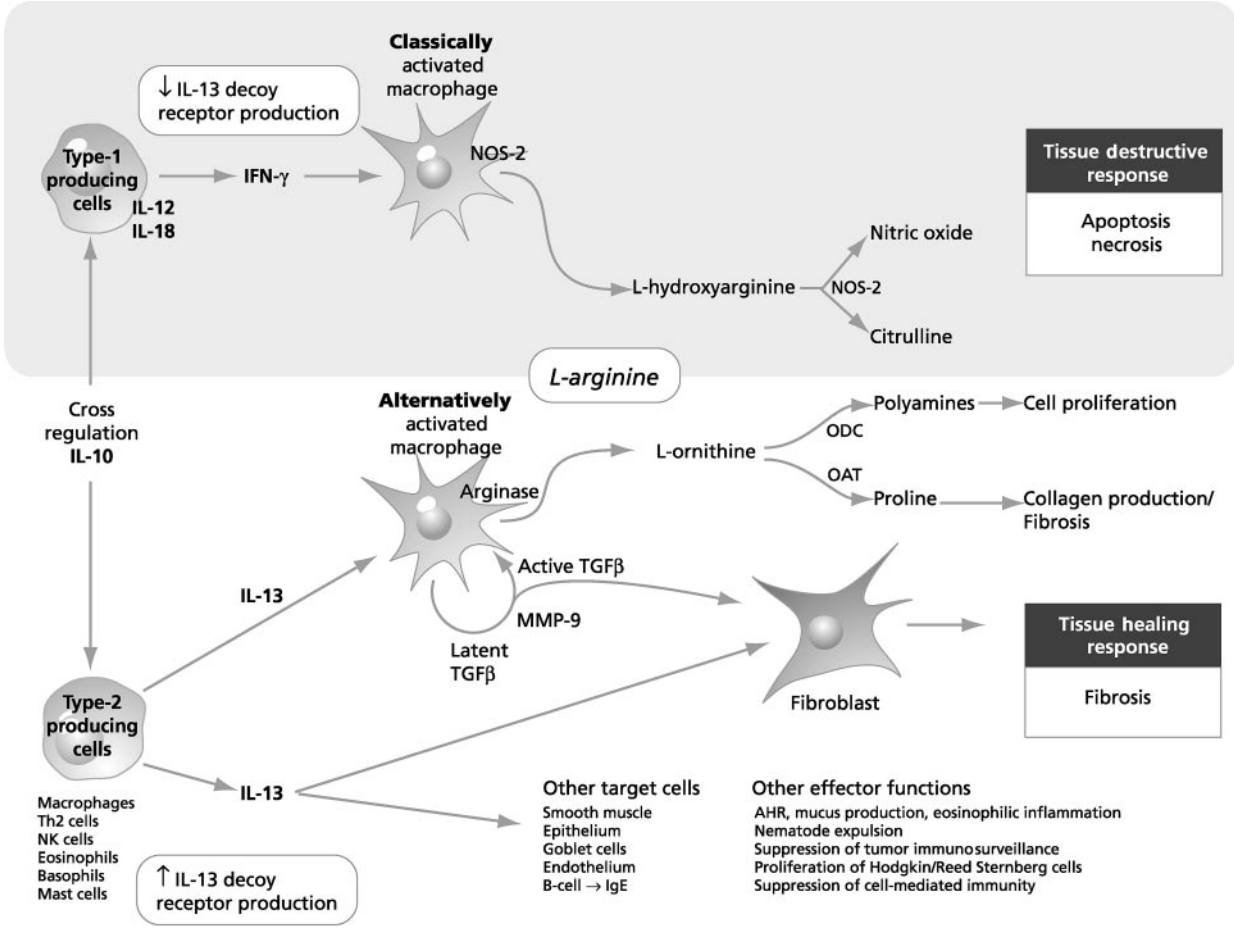

remodeling and fibrosis are important pathological features in a variety of disorders where type-2 cytokines dominate, including asthma (9, 55), idiopathic pulmonary fibrosis (133), chronic graft rejection (134), bleomycin-induced pulmonary fibrosis (135), progressive systemic sclerosis (136), radiation-induced pulmonary fibrosis (137), and hepatic fibrosis (123, 125). Therefore, IL-13 antagonists may prove highly effective in a variety of situations where chronic exposure to IL-13 triggers excessive healing, tissue remodeling, or the formation of destructive tissue pathology.

REGULATION AND SUPPRESSION OF IL-13-MEDIATED EFFECTOR FUNCTION

The studies discussed above illustrate the pivotal role of IL-13 in the regulation of type-2 cytokine-mediated immune responses. In some pathological conditions, IL-13 is either under- or overexpressed resulting in decreased resistance to infection, uncontrolled tumor cell growth, severe asthma, or destructive inflammation and tissue scarring. Thus, understanding the molecular mechanisms that govern the expression and/or functional activity of IL-13 is of critical importance. Several inhibitory pathways have been described, which may offer novel therapeutic strategies to treat infectious, malignant, and inflammatory diseases. The following sections outline a few of the important endogenous IL-13 regulatory systems.

IL-4

IL-4 is the central differentiation factor for Th2 response development (138). In the absence of IL-4, Th2 responses are significantly impaired, although, in some studies, low yet significant production of IL-5 and IL-13 has been reported, even in the absence of the IL-4 receptor and Stat6 signaling molecule (6, 139, 140). In contrast, IL-13 is not thought to play a significant role primarily because T cells lack the appropriate receptors (141, 142). Nevertheless, IL-13 may participate indirectly because impaired Th2 response generation was also reported in some but not all studies utilizing IL-13 knockout mice (12, 26, 125). The discovery of IL-4-independent IL-13 production, however, was significant because it provided one of the first clues that IL-13 might be the critical Th2 effector cytokine in vivo. It also helped explain some of the divergent findings reported with IL-4- and IL-4Rα-deficient mice. Indeed, although IL-13 production is markedly decreased in the absence of IL-4, the residual IL-13 response remains highly active as explained in many of the disease models discussed above (8, 43, 48, 56, 88, 123). Even a small amount of IL-13 is sufficient to mediate many of its in vivo effector functions. In the murine schistosomiasis model, for example, IL-13 production decreases over 80% in the absence of IL-4 (123). Nevertheless, granuloma formation proceeds normally in these IL-4-deficient animals unless IL-13 is also neutralized. Thus, although targeting IL-4 will likely yield a lower IL-13 response, in many

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situations both cytokines must be neutralized to effectively block effector activity completely. This may account for the efficacy of soluble IL-4 receptor for the treatment of moderate persistent asthma (143). IL-13 is produced at much greater levels than IL-4, which may also explain why IL-13 operates as the key effector cytokine in vivo (16, 45, 46, 54, 123).

IL-12, IL-18, IFN-γ, and Immunostimulatory CpG Oligodeoxynucleotides

Many of the cytokines and mediators that drive Th1 cell development are potent inhibitors of IL-13 production and/or activity. This was perhaps exemplified best in early studies examining the mechanisms of nematode expulsion, asthma, and schistosome egg-induced granuloma formation. In schistosomiasis, the pulmonary egg-induced granulomatous response evolves from an early Th0-like phase to a strong Th2 response, which peaks approximately 7 to 10 days post-primary iv egg challenge (113, 114). In the early phase, high levels of IFN-γ and IL-12 are detectable; both cytokines play important regulatory roles. IL-12 is a potent stimulus for T cell– and NK cell–derived IFN-γ and inhibits T cell production of IL-4 (144). In support of these observations, mAb depletion of IFN-γ or IL-12 augmented IL-4/IL-13 levels and increased pulmonary granuloma formation (61). A similar enhancement was observed when antiasialo GM1 antibodies were administered, which suggested the early IFN-γ response was derived from an NK cell source. In contrast, exogenous treatment with rIL-12 profoundly inhibited primary granuloma formation and IL-4/IL-13 production, while increasing IFN-γ and IL-12 levels. IFN-γ was of critical importance because similar IL-12 treatments in IFN-γ-deficient mice not only failed to inhibit granuloma formation but also actually caused a marked exacerbation in the response (145). Similar results were generated with the *N. brasiliensis* model, where exogenous IL-12 inhibited parasite expulsion and anti-IFN-γ mAb treatment blocked IL-12 activity (146). Exogenous IL-12 also reduced secondary granuloma formation and IL-13 production in schistosome egg-sensitized mice, which demonstrated a role for the cytokine in reversing established Th2-type responses (61). Mice immunized with egg antigens plus IL-12, to establish a memory Th1 response, were also protected from secondary granuloma formation (61), and, more importantly, displayed a marked reduction in IL-13-induced fibrosis when subsequently infected (115). These findings suggested that IL-12 provides an effective strategy to prophylactically inhibit IL-13-driven pathologies.

In agreement with the parasite models, IL-12 inhibits antigen-induced airway hyperresponsiveness, inflammation, and Th2 cytokine expression in a mouse model of asthma (147). Here again, the effects of IL-12 were dependent on IFN-γ because concurrent treatment with IL-12 and anti-IFN-γ mAb partially reversed the inhibition of airway hyperresponsiveness and eosinophilia by IL-12. There was also evidence that IL-12 was active during ongoing secondary responses, which provides further proof that IL-12 and immune-deviation might be highly effective

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for the treatment of allergic disease. Similar changes were observed when IL-12 was substituted with CpG oligodeoxynucleotides (CpG ODN) (148, 149), which are potent inducers of Th1-associated cytokines (150). In each case, the protective effects were highly dependent on the induction of IFN-γ and simultaneous suppression of IL-13 activity (124, 151).

Given that IL-18 was originally described as an interferon-gamma-inducing factor (IGIF) (152), it was probably not unexpected that IL-18 showed potent Th2-inhibiting activity (153–155). Nevertheless, the role of IL-18 in the regulation of Th2 responses remains somewhat controversial (156). IL-18 is secreted by activated macrophages and can act synergistically with IL-12 to induce high levels of IFN-γ production in T cells (152). Consistent with its role as a Th1-inducing cytokine, treatment of OVA-sensitized mice with exogenous IL-18 or with an IL-18-expressing adenovirus reduced allergen-specific airway eosinophilia (154), IL-4 production, and mucus hypersecretion; increased IFN-γ; and prevented the development of AHR (155). In contrast, mice deficient in IL-18 showed an enhancement in allergen-induced eosinophilia (154). The effects of IL-18 were also highly dependent on IFN-γ and IL-12 (155), which provides evidence of a regulatory loop in which IL-12 and IL-18 act in concert with IFN-γ to antagonize the allergy-inducing activities of IL-13. Nevertheless, this inhibitory activity may depend on the cytokine milieu (156). Indeed, other studies suggest that IL-18 may exhibit Th2-promoting activities (157–160), particularly when produced in the absence of IL-12. In one study, basophils and mast cells expressed IL-18 receptors and produced large amounts of IL-4 and IL-13 when stimulated with IL-3 and IL-18 (157). A similar response was also observed when IL-18 was injected in vivo. The addition of IL-12, however, blocked the type-2 cytokine promoting activity of IL-18 and in an IFN-γ-dependent fashion. Consistent with these findings, administration of IL-18 in conjunction with allergic sensitization and challenge increased serum levels of IgE and splenocyte production of Th2-type cytokines (159). Moreover, while eosinophil recruitment decreased early after IL-18 treatment, as the response matured, lung eosinophilia increased dramatically, which demonstrated again that IL-18 was promoting a Th2-type response in vivo. The IL-18-induced IgE response was also $CD4^+$ T cell-, IL-4-, and Stat6-dependent (158), and in a related study, eosinophil recruitment triggered by IL-18 was at least partially dependent on TNF-α (160).

Nevertheless, it should be emphasized again that in some settings, IL-18 exhibits potent Th2-suppressing activity. In the *T. muris* model, resistance clearly depends on IL-4 and IL-13, and mice treated with IL-18 displayed decreased IL-4/IL-13 levels (161). It is surprising, however, that the IL-18-treated animals failed to develop an upregulated IFN-γ response, and IFN-γ-deficient mice remained susceptible to the Th2-suppressing activities of IL-18, which suggested IL-18 might directly inhibit IL-4 and IL-13 (161). Thus, when viewed together, the results from all of these studies clearly indicate that, under the right circumstances, IL-18 may either inhibit or promote IL-13 activity. The factors that influence this decision, however, remain unclear, although IL-12 may be a key player.

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TNF-α

Like IL-18, the role of TNF-α may be context dependent in that it has been shown to both promote and antagonize IL-13-driven responses. In the *T. muris* model, in vivo blockade of TNF-α in mice that normally mount a protective IL-4/IL-13 response significantly delayed worm expulsion for the duration of the treatment (28). IL-13-mediated worm expulsion in IL-4-deficient mice was also TNF-α dependent and enhanced by exogenous treatment with TNF-α. TNF receptor-deficient mice were also more susceptible, and there was evidence that the protective Th2 response was being skewed to a susceptible Th1 phenotype in the absence of TNF-α signaling (28). The results from these studies were the first to demonstrate a role for TNF-α in regulating Th2-type cytokine responses at mucosal sites. They were also the first to directly implicate TNF-α as an important protective cytokine during helminth infection. Nevertheless, the protection mediated by TNF-α appears to be entirely attributable to its Th2-promoting activity because high levels of TNF-α are produced in Th1-deviated mice; and yet, these mice remain highly susceptible to *T. muris* infection (33). In schistosomiasis, granuloma formation and fibrosis are also IL-4/IL-13-dependent and reduced in mice pretreated with schistosome eggs and IL-12 (115). However, if TNF-α is neutralized at the time of egg laying, IL-4/IL-13 production, granuloma formation, and fibrosis are rapidly restored, which suggests TNF-α is necessary to maintain the protective Th1 response (162). Nevertheless, TNF-α is also expressed in mice exhibiting highly skewed Th2-type responses (119), and studies of human schistosomiasis suggest it may be contributing to the development of periportal fibrosis (163). Thus, under the right circumstances, TNF-α can exhibit either Th1- or Th2-promoting activities. The contribution of TNF-α to the regulation of IL-13-driven responses, therefore, appears to be influenced greatly by the cytokine milieu.

IL-10

IL-10 was initially described as a Th2-type cytokine that antagonizes Th1 cell development by suppressing IL-12 and IFN-γ production (164). Nevertheless, it has become increasingly clear that IL-10 exhibits potent immunosuppressive activity during both Th1- and Th2-dominant immune responses (165, 166). In the absence of IL-10, mice infected with *S. mansoni* displayed a mixed Th1/Th2-type cytokine response (167). However, mice deficient in both IL-10 and IL-12 (119) or IL-10 and IFN-γ (168) developed highly polarized and exaggerated type-2 cytokine responses, with IL-13 levels approaching 10-fold higher than WT. Consequently, fibrogenesis also increased dramatically in these double cytokine-deficient animals (119, 168). These studies showed that IL-10 and the type-1-inducing cytokines IL-12 and IFN-γ cooperate to suppress type-2 cytokine-driven inflammation. Thus, mice displaying high IL-13 and low IL-10/IFN-γ responses tend to exhibit the greatest IL-13-mediated effector activity (124). Similar conclusions were drawn in studies investigating gastrointestinal parasite expulsion and asthma (33, 151). In fact, in the experimental asthma model, IL-10, rather than the counter-regulatory

type-1 cytokine response, was hypothesized to provide the primary mechanism by which allergic inflammatory processes in the lungs are inhibited (169, 170). This is consistent with the observation that few Th1-effector cells are found in the lungs of healthy people, whereas IL-10 levels are lower in patients with asthma (170). Thus, normal production of IL-10 in nonasthmatic people, rather than a protective type-1 response, may be the key factor limiting IL-4/IL-13-mediated inflammatory processes. IL-10 may also help explain the hygiene hypothesis, which suggests the increase in allergic inflammation and asthma observed in westernized countries is due to a cleaner environment and decreased incidence of childhood infections (171, 172). Indeed, decreased atopy was reported in children infected with *S. haematobium*, and this was associated with higher concentrations of antigen-specific IL-10 (173). Thus, antiinflammatory cytokines induced during long-term chronic infections appear to provide protection from allergic inflammation (174). Recent studies suggest regulatory T cells producing IL-10 and/or TGF-β may also play an essential inhibitory role (175, 176). Dendritic cells exposed to respiratory antigen transiently produced IL-10 and stimulated the development of IL-10-producing $CD4^+$ T regulatory cells (175). Thus, induction of tolerance by IL-10 may provide an effective means to reduce AHR and asthma. Nevertheless, it is important to note other studies examining the function of IL-10 found that AHR (177, 178), eosinophilic inflammation, and Th2 effector function can also be increased by IL-10 (179). Similar findings were reported in the *T. muris* model, where IL-10 promoted IL-4/IL-13-mediated parasite expulsion by suppressing the counter-regulatory type-1 cytokine response (33). Therefore, additional study is needed before IL-10 or regulatory T cells can be advocated as a therapy for asthma or other IL-4/IL-13-driven disorders.

TGF-β

Like IL-10, TGF-β both antagonizes and promotes IL-13 effector function. As indicated above, regulatory T cells producing TGF-β and/or IL-10 provide significant protection from IL-13-dependent allergic inflammation (175, 176). Nevertheless, recent studies indicate TGF-β is also an important downstream mediator of IL-13-induced activity. One of the more significant effector functions of IL-13 is the promotion of wound healing and fibrosis (9, 123, 180, 181). A recent study showed IL-13 induces fibrosis by selectively stimulating and activating the fibrogenic cytokine TGF-β (127). In this study, macrophages were the major site of TGF-β production (127), although a second study suggested bronchial epithelial cells may be another important source (182). Activation of TGF-β was mediated by an IL-13, a plasmin/serine protease, and an MMP-9-dependent mechanism. TGF-β antagonists were also highly effective at ameliorating the IL-13-induced pulmonary fibrosis (127). As such, these observations suggest an indirect TGF-β-dependent role for IL-13 in the development of fibrosis. Nevertheless, IL-13 directly stimulates collagen deposition in fibroblasts cultured in vitro (123, 181). Moreover, recent unpublished work in the schistosomiasis model showed that liver fibrosis can develop in the absence of MMP-9, TGF-β, and Smad-3 signaling pathways (M. Kaviratne, M. Hesse, A.W. Cheever, J. Letterio, M. Leusink, A. Roberts,

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S. Davies, L. Wakefield, T.A. Wynn, unpublished observations). These latter observations suggest a TGF-β-independent but IL-13-dependent pathway may also exist. Therefore, further study is needed to elucidate the common and distinct fibrogenic pathways triggered by IL-13 and TGF-β.

The Decoy IL-13 Receptor Alpha 2

In many of the disease models discussed above, IL-13 is produced at much higher levels than IL-4, which may, in part, explain why it acts as the central Th2-effector cytokine. Nevertheless, the receptors that bind these cytokines may also have a significant impact on their functional activity in vivo. The receptor-binding chains for IL-13 include IL-13Rα1 and IL-13Rα2 (15, 183–185). When expressed alone, IL-13Rα1 binds IL-13 with low affinity. However, when IL-13Rα1 is coexpressed with IL-4Rα, a high-affinity receptor-signaling complex is formed (183, 185). This receptor complex is expressed widely on both lymphoid and nonlymphoid cells and can also be activated by IL-4, thus accounting for the functional overlap between IL-4 and IL-13 (186). The second IL-13 binding chain, IL-13Rα2, binds IL-13 with high affinity and, in contrast to IL-13Rα1, is also found as a soluble receptor in mouse serum and urine (15, 187). Structural differences between the cytoplasmic domains of the IL-13 receptors, however, suggest they are functionally distinct. The cytoplasmic region of murine IL-13Rα2 does not possess an obvious signaling motif or JAK/STAT binding sequence (15), which raises the possibility that it is a dominant negative inhibitor or decoy receptor, as originally described for the IL-1 receptor type II (188).

To understand the role of IL-13Rα2 in regulating the biological activity of IL-13, mice with targeted deletion of IL-13Rα2 were recently generated (N. Wood, M. Whitters, B.A. Jacobson, J. Witek, J.P. Sypek, M. Kasaian, M. Eppihimer, M. Unger, S. Goldman, M. Collins, D.D. Donaldson, M. Grusby, submitted manuscript). Basal serum IgE levels were elevated in IL-13R$\alpha2^{-/-}$ mice despite the fact that serum IL-13 was absent and IFN-γ production increased compared to WT mice. The frequency of bone marrow macrophage progenitors also increased in the knockout animals, whereas the ability of tissue macrophages to produce NO and IL-12 in response to LPS decreased substantially (N. Wood, M. Whitters, B.A. Jacobson, J. Witek, J.P. Sypek, M. Kasaian, M. Eppihimer, M. Unger, S. Goldman, M. Collins, D.D. Donaldson, M. Grusby, submitted manuscript). From these studies, the authors concluded that the primary function of the IL-13Rα2 is to limit IL-13 effector function in vivo (Figure 1).

IL-13Rα2 deficiency was also studied in the murine schistosomiasis model, where chronic exposure to IL-13 is the principle cause of liver fibrosis (M.G. Chiaramonte, M. Mentink-Kane, B.A. Jacobson, A.W. Cheever, M.J. Whitters, submitted manuscript). The mechanisms regulating expression of IL-13Rα2 in vivo were also examined. Basal expression of IL-13Rα2 mRNA was nearly undetectable in the livers of uninfected mice. However, shortly after the onset of egg-laying, a marked induction of IL-13Rα2 expression was observed, which persisted throughout the chronic stage of infection and correlated almost perfectly with the development of liver fibrosis. Receptor expression was also highly

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dependent on IL-10, IL-13, and Stat6 and inhibited by the Th1-inducing adjuvant IL-12, thus showing a strong correlation with the egg-induced Th2 response (M.G. Chiaramonte, M. Mentink-Kane, B.A. Jacobson, A.W. Cheever, M.J. Whitters, submitted manuscript). Schistosome-infected IL-13Rα2-deficient mice showed a marked exacerbation in hepatic fibrosis, despite displaying no change in granulomatous inflammation, tissue eosinophilia, or mastocytosis. Fibrosis increased despite the fact that IL-13 levels decreased significantly, thus supporting findings from unchallenged mice (N. Wood, M. Whitters, B.A. Jacobson, J. Witek, J.P. Sypek, M. Kasaian, M. Eppihimer, M. Unger, S. Goldman, M. Collins, D.D. Donaldson, M. Grusby, submitted manuscript). Pathology was prevented when IL-13Rα2-deficient mice were treated with a soluble IL-13Rα2-Fc construct (M.G. Chiaramonte, M. Mentink-Kane, B.A. Jacobson, A.W. Cheever, M.J. Whitters, submitted manuscript), formally demonstrating that their exacerbated fibrotic response was due to heightened IL-13 activity. As such, these studies illustrate a novel and previously unappreciated mechanism for limiting pathology associated with chronic IL-13-mediated inflammatory responses. Indeed, effective exploitation of this endogenous IL-13 dampening system has already been achieved in several experimental models (54, 56, 57, 63, 88, 123, 124).

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SUMMARY

IL-13 is produced by and either directly or indirectly affects the function of multiple cell types, including T cells, eosinophils, mast cells, basophils, epithelial cells, smooth muscle cells, fibroblasts, and macrophages. The published literature on this area alone was much too broad to adequately cover in one review. However, this more focused area of research on IL-13 is extremely important and will certainly remain an exciting topic in the coming years. What cell types produce IL-13 and under what conditions? Who are the responding cells? What regulates IL-4/IL-13 receptor expression, and how does this affect the functional activity of IL-13? What role does the IL-13 decoy receptor play in other diseases, and how is the functional activity of IL-4 and IL-13 regulated? These are just a few of the important questions that remain unclear. The type-2 response was originally thought of as a counter-regulatory system for the type-1 immune response (189). Nevertheless, the recent explosion in research on IL-13 clearly demonstrates this is an extreme oversimplification. Given its central status in the Th2 response, a complete understanding of the many effector functions of IL-13 is needed so that it can be effectively exploited for therapeutic intervention.

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LITERATURE CITED

1. Minty A, Chalon P, Derocq JM, Dumont X, Guillemot JC, et al. 1993. Interleukin-13 is a new human lymphokine regulating inflammatory and immune responses. *Nature* 362:248–50
2. McKenzie AN, Culpepper JA, de Waal Malefyt R, Briere F, Punnonen J, et al. 1993. Interleukin 13, a T-cell-derived cytokine that regulates human monocyte and B-cell function. *Proc. Natl. Acad. Sci. USA* 90:3735–40
3. Punnonen J, Aversa G, Cocks BG, McKenzie ANJ, Menon S, et al. 1993. Interleukin 13 induces interleukin 4–independent IgG4 and IgE synthesis and CD23 expression in human B cells. *Proc. Natl. Acad. Sci. USA* 90:3730–34
4. Kaplan MH, Schindler U, Smiley ST, Grusby MJ. 1996. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity* 4:313–19
5. Takeda K, Tanaka T, Shi W, Matsumoto M, Minami M, et al. 1996. Essential role of Stat6 in IL-4 signalling. *Nature* 380:627–30
6. Noben-Trauth N, Shultz LD, Brombacher F, Urban JF Jr, Gu H, et al. 1997. An interleukin 4 (IL-4)-independent pathway for CD4 + T cell IL-4 production is revealed in IL-4 receptor-deficient mice. *Proc. Natl. Acad. Sci. USA* 94:10838–43
7. Barner M, Mohrs M, Brombacher F, Kopf M. 1998. Differences between IL-4R alpha-deficient and IL-4-deficient mice reveal a role for IL-13 in the regulation of Th2 responses. *Curr. Biol.* 8:669–72
8. Urban JF Jr, Noben-Trauth N, Donaldson DD, Madden KB, Morris SC, et al. 1998. IL-13, IL-4Ralpha, and Stat6 are required for the expulsion of the gastrointestinal nematode parasite Nippostrongylus brasiliensis. *Immunity* 8:255–64
9. Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, et al. 1999. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J. Clin. Invest.* 103:779–88
10. Emson CL, Bell SE, Jones A, Wisden W, McKenzie AN. 1998. Interleukin (IL)-4-independent induction of immunoglobulin (Ig)E, and perturbation of T cell development in transgenic mice expressing IL-13. *J. Exp. Med.* 188:399–404
11. McKenzie GJ, Bancroft A, Grencis RK, McKenzie AN. 1998. A distinct role for interleukin-13 in Th2-cell-mediated immune responses. *Curr. Biol.* 8:339–42
12. McKenzie GJ, Emson CL, Bell SE, Anderson S, Fallon P, et al. 1998. Impaired development of Th2 cells in IL-13-deficient mice. *Immunity* 9:423–32
13. McKenzie GJ, Fallon PG, Emson CL, Grencis RK, McKenzie AN. 1999. Simultaneous disruption of interleukin (IL)-4 and IL-13 defines individual roles in T helper cell type 2-mediated responses. *J. Exp. Med.* 189:1565–72
14. Debinski W, Obiri NI, Pastan I, Puri RK. 1995. A novel chimeric protein composed of interleukin 13 and Pseudomonas exotoxin is highly cytotoxic to human carcinoma cells expressing receptors for interleukin 13 and interleukin 4. *J. Biol. Chem.* 270:16775–80
15. Donaldson DD, Whitters MJ, Fitz LJ, Neben TY, Finnerty H, et al. 1998. The murine IL-13 receptor alpha 2: molecular cloning, characterization, and comparison with murine IL-13 receptor alpha 1. *J. Immunol.* 161:2317–24
16. Ruth JH, Warmington KS, Shang X, Lincoln P, Evanoff H, et al. 2000. Interleukin 4 and 13 participation in mycobacterial (type-1) and schistosomal (type-2) antigen-elicited pulmonary granuloma formation: multiparameter analysis of

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cellular recruitment, chemokine expression and cytokine networks. *Cytokine* 12:432–44
17. Guo L, Hu-Li J, Zhu J, Pannetier C, Watson C, et al. 2001. Disrupting Il13 impairs production of IL-4 specified by the linked allele. *Nat. Immunol.* 2:461–66
18. Finkelman FD, Shea-Donohue T, Goldhill J, Sullivan CA, Morris SC, et al. 1997. Cytokine regulation of host defense against parasitic gastrointestinal nematodes: lessons from studies with rodent models. *Annu. Rev. Immunol.* 15:505–33
19. Katona IM, Urban JF Jr, Finkelman FD. 1988. The role of L3T4+ and Lyt-2+ T cells in the IgE response and immunity to Nippostrongylus brasiliensis. *J. Immunol.* 140:3206–11
20. Kopf M, Le Gros G, Bachmann M, Lamers MC, Bluethmann H, et al. 1993. Disruption of the murine IL-4 gene blocks Th2 cytokine responses. *Nature* 362:245–48
21. Madden KB, Urban JF Jr, Ziltener HJ, Schrader JW, Finkelman FD, et al. 1991. Antibodies to IL-3 and IL-4 suppress helminth-induced intestinal mastocytosis. *J. Immunol.* 147:1387–91
22. Urban JF Jr, Maliszewski CR, Madden KB, Katona IM, Finkelman FD. 1995. IL-4 treatment can cure established gastrointestinal nematode infections in immunocompetent and immunodeficient mice. *J. Immunol.* 154:4675–84
23. Urban JF Jr, Noben-Trauth N, Schopf L, Madden KB, Finkelman FD. 2001. Cutting edge: IL-4 receptor expression by non-bone marrow-derived cells is required to expel gastrointestinal nematode parasites. *J. Immunol.* 167:6078–81
24. Grencis RK. 2001. Cytokine regulation of resistance and susceptibility to intestinal nematode infection—from host to parasite. *Vet. Parasitol.* 100:45–50
25. Finkelman FD, Wynn TA, Donaldson DD, Urban JF Jr. 1999. The role of IL-13 in helminth-induced inflammation and protective immunity against nematode infections. *Curr. Opin. Immunol.* 11:420–26
26. Bancroft AJ, McKenzie AN, Grencis RK. 1998. A critical role for IL-13 in resistance to intestinal nematode infection. *J. Immunol.* 160:3453–61
27. Bancroft AJ, Artis D, Donaldson DD, Sypek JP, Grencis RK. 2000. Gastrointestinal nematode expulsion in IL-4 knockout mice is IL-13 dependent. *Eur. J. Immunol.* 30:2083–91
28. Artis D, Humphreys NE, Bancroft AJ, Rothwell NJ, Potten CS, et al. 1999. Tumor necrosis factor alpha is a critical component of interleukin 13-mediated protective T helper cell type 2 responses during helminth infection. *J. Exp. Med.* 190:953–62
29. Urban J, Fang H, Liu Q, Ekkens MJ, Chen SJ, et al. 2000. IL-13-mediated worm expulsion is B7 independent and IFN-gamma sensitive. *J. Immunol.* 164:4250–56
30. Urban JF Jr, Schopf L, Morris SC, Orekhova T, Madden KB, et al. 2000. Stat6 signaling promotes protective immunity against Trichinella spiralis through a mast cell- and T cell-dependent mechanism. *J. Immunol.* 164:2046–52
31. Khan WI, Vallance BA, Blennerhassett PA, Deng Y, Verdu EF, et al. 2001. Critical role for signal transducer and activator of transcription factor 6 in mediating intestinal muscle hypercontractility and worm expulsion in Trichinella spiralis-infected mice. *Infect. Immun.* 69:838–44
32. Shea-Donohue T, Sullivan C, Finkelman FD, Madden KB, Morris SC, et al. 2001. The role of IL-4 in Heligmosomoides polygyrus-induced alterations in murine intestinal epithelial cell function. *J. Immunol.* 167:2234–39
33. Schopf LR, Hoffmann KF, Cheever AW, Urban JF Jr, Wynn TA. 2002. IL-10 is critical for host resistance and survival during gastrointestinal helminth infection. *J. Immunol.* 168:2383–92
34. Khan WI, Blennerhasset P, Ma C,

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Matthaei KI, Collins SM. 2001. Stat6 dependent goblet cell hyperplasia during intestinal nematode infection. *Parasite Immunol.* 23:39–42

35. Akiho H, Blennerhassett P, Deng YK, Collins SM. 2002. Role of IL-4, IL-13, and STAT6 in inflammation-induced hypercontractility of murine smooth muscle cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* 282:G226–32
36. Madden KB, Whitman L, Sullivan C, Finkelman FD, Gause WC, et al. 2002. Role of Stat6 and mast cells in IL-4- and IL-13-induced alterations in murine intestinal epithelial cell function. *J. Immunol.* 169:4417–22
37. Zhao A, Mulloy D, Urban JF Jr, Gause WC, Shea-Donohue T. 2001. Role of Stat6 in hypercontractility of murine small intestinal smooth muscle induced by nematode infection. *Gastroenterology* 120:A534
38. Reiner SL, Locksley RM. 1995. The regulation of immunity to Leishmania major. *Annu. Rev. Immunol.* 13:151–77
39. Belkaid Y, Hoffmann KF, Mendez S, Kamhawi S, Udey MC, et al. 2001. The role of interleukin (IL)-10 in the persistence of Leishmania major in the skin after healing and the therapeutic potential of anti-IL-10 receptor antibody for sterile cure. *J. Exp. Med.* 194:1497–506
40. Mock B, Blackwell J, Hilgers J, Potter M, Nacy C. 1993. Genetic control of Leishmania major infection in congenic, recombinant inbred and F2 populations of mice. *Eur. J. Immunogenet.* 20:335–48
41. Beebe AM, Mauze S, Schork NJ, Coffman RL. 1997. Serial backcross mapping of multiple loci associated with resistance to Leishmania major in mice. *Immunity* 6:551–57
42. Demant P, Lipoldova M, Svobodova M. 1996. Resistance to Leishmania major in mice. *Science* 274:1392–93
43. Noben-Trauth N, Paul WE, Sacks DL. 1999. IL-4- and IL-4 receptor-deficient BALB/c mice reveal differences in susceptibility to Leishmania major parasite substrains. *J. Immunol.* 162:6132–40
44. Sosa MR, Rosas LE, McKenzie AN, Satoskar AR. 2001. IL-13 gene-deficient mice are susceptible to cutaneous L. mexicana infection. *Eur. J. Immunol.* 31:3255–60
45. Bourreau E, Prevot G, Pradinaud R, Launois P. 2001. Interleukin (IL)-13 is the predominant Th2 cytokine in localized cutaneous leishmaniasis lesions and renders specific CD4+ T cells unresponsive to IL-12. *J. Infect. Dis.* 183:953–59
46. Babaloo Z, Kaye PM, Eslami MB. 2001. Interleukin-13 in Iranian patients with visceral leishmaniasis: relationship to other Th2 and Th1 cytokines. *Trans. R. Soc. Trop. Med. Hyg.* 95:85–88
47. Kopf M, Brombacher F, Kohler G, Kienzle G, Widmann KH, et al. 1996. IL-4-deficient Balb/c mice resist infection with Leishmania major. *J. Exp. Med.* 184:1127–36
48. Mohrs M, Ledermann B, Kohler G, Dorfmuller A, Gessner A, et al. 1999. Differences between IL-4- and IL-4 receptor alpha-deficient mice in chronic leishmaniasis reveal a protective role for IL-13 receptor signaling. *J. Immunol.* 162:7302–8
49. Matthews DJ, Emson CL, McKenzie GJ, Jolin HE, Blackwell JM, et al. 2000. IL-13 is a susceptibility factor for Leishmania major infection. *J. Immunol.* 164:1458–62
50. Dent AL, Doherty TM, Paul WE, Sher A, Staudt LM. 1999. BCL-6-deficient mice reveal an IL-4-independent, STAT6-dependent pathway that controls susceptibility to infection by Leishmania major. *J. Immunol.* 163:2098–103
51. Alexander J, Brombacher F, McGachy A, Scott P, McKenzie ANJ, et al. 2002. An essential role for IL-13 in maintaining a non-healing response following *Leishamani mexicana* infection. *Eur. J. Immunol.* 32:2923-33
52. Gorelik L, Constant S, Flavell RA. 2002. Mechanism of transforming growth factor

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beta-induced inhibition of T helper type 1 differentiation. *J. Exp. Med.* 195:1499–505

53. Flesch IE, Wandersee A, Kaufmann SH. 1997. Effects of IL-13 on murine listeriosis. *Int. Immunol.* 9:467–74
54. Chiaramonte MG, Schopf LR, Neben TY, Cheever AW, Donaldson DD, et al. 1999. IL-13 is a key regulatory cytokine for Th2 cell-mediated pulmonary granuloma formation and IgE responses induced by Schistosoma mansoni eggs. *J. Immunol.* 162:920–30
55. Blease K, Jakubzick C, Westwick J, Lukacs N, Kunkel SL, et al. 2001. Therapeutic effect of IL-13 immunoneutralization during chronic experimental fungal asthma. *J. Immunol.* 166:5219–24
56. Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, et al. 1998. Interleukin-13: central mediator of allergic asthma. *Science* 282:2258–61
57. Grunig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, et al. 1998. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 282:2261–63
58. Fallon PG, Emson CL, Smith P, McKenzie AN. 2001. IL-13 overexpression predisposes to anaphylaxis following antigen sensitization. *J. Immunol.* 166:2712–16
59. Corne J, Chupp G, Lee CG, Homer RJ, Zhu Z, et al. 2000. IL-13 stimulates vascular endothelial cell growth factor and protects against hyperoxic acute lung injury. *J. Clin. Invest.* 106:783–91
60. Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, et al. 2000. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. *J. Clin. Invest.* 106:1081–93
61. Wynn TA, Eltoum I, Oswald IP, Cheever AW, Sher A. 1994. Endogenous interleukin 12 (IL-12) regulates granuloma formation induced by eggs of Schistosoma mansoni and exogenous IL-12 both inhibits and prophylactically immunizes against egg pathology. *J. Exp. Med.* 179:1551–61
62. Cohn L, Tepper JS, Bottomly K. 1998. IL-4-independent induction of airway hyperresponsiveness by Th2, but not Th1, cells. *J. Immunol.* 161:3813–16
63. Morse B, Sypek JP, Donaldson DD, Haley KJ, Lilly CM. 2002. Effects of IL-13 on airway responses in the guinea pig. *Am. J. Physiol. Lung Cell Mol. Physiol.* 282:L44–49
64. Kuperman D, Schofield B, Wills-Karp M, Grusby MJ. 1998. Signal transducer and activator of transcription factor 6 (Stat6)-deficient mice are protected from antigen-induced airway hyperresponsiveness and mucus production. *J. Exp. Med.* 187:939–48
65. Akimoto T, Numata F, Tamura M, Takata Y, Higashida N, et al. 1998. Abrogation of bronchial eosinophilic inflammation and airway hyperreactivity in signal transducers and activators of transcription (STAT)6-deficient mice. *J. Exp. Med.* 187: 1537–42
66. Cohn L, Homer RJ, MacLeod H, Mohrs M, Brombacher F, et al. 1999. Th2-induced airway mucus production is dependent on IL-4Ralpha, but not on eosinophils. *J. Immunol.* 162:6178–83
67. Yang M, Hogan SP, Henry PJ, Matthaei KI, McKenzie AN, et al. 2001. Interleukin-13 mediates airways hyperreactivity through the IL-4 receptor-alpha chain and STAT-6 independently of IL-5 and eotaxin. *Am. J. Respir. Cell Mol. Biol.* 25:522–30
68. Venkayya R, Lam M, Willkom M, Grunig G, Corry DB, et al. 2002. The Th2 lymphocyte products IL-4 and IL-13 rapidly induce airway hyperresponsiveness through direct effects on resident airway cells. *Am. J. Respir. Cell. Mol. Biol.* 26:202–8
69. Jordan NJ, Watson ML, Williams RJ, Roach AG, Yoshimura T, et al. 1997. Chemokine production by human

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vascular smooth muscle cells: modulation by IL-13. *Br. J. Pharmacol.* 122:749–57

70. Wei LH, Jacobs AT, Morris SM Jr, Ignarro LJ. 2000. IL-4 and IL-13 upregulate arginase I expression by cAMP and JAK/STAT6 pathways in vascular smooth muscle cells. *Am. J. Physiol. Cell Physiol.* 279:C248–56
71. Laporte JC, Moore PE, Baraldo S, Jouvin MH, Church TL, et al. 2001. Direct effects of interleukin-13 on signaling pathways for physiological responses in cultured human airway smooth muscle cells. *Am. J. Respir. Crit. Care Med.* 164: 141–48
72. Mehlhop PD, van de Rijn M, Goldberg AB, Brewer JP, Kurup VP, et al. 1997. Allergen-induced bronchial hyperreactivity and eosinophilic inflammation occur in the absence of IgE in a mouse model of asthma. *Proc. Natl. Acad. Sci. USA* 94:1344–49
73. Webb DC, McKenzie AN, Koskinen AM, Yang M, Mattes J, et al. 2000. Integrated signals between IL-13, IL-4, and IL-5 regulate airways hyperreactivity. *J. Immunol.* 165:108–13
74. Walter DM, McIntire JJ, Berry G, McKenzie AN, Donaldson DD, et al. 2001. Critical role for IL-13 in the development of allergen-induced airway hyperreactivity. *J. Immunol.* 167:4668–75
75. Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, et al. 2001. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *J. Allergy Clin. Immunol.* 108:594–601
76. Mattes J, Yang M, Mahalingam S, Kuehr J, Webb DC, et al. 2002. Intrinsic defect in T cell production of interleukin (IL)-13 in the absence of both IL-5 and eotaxin precludes the development of eosinophilia and airways hyperreactivity in experimental asthma. *J. Exp. Med.* 195:1433–44
77. Mattes J, Yang M, Siqueira A, Clark K, MacKenzie J, et al. 2001. IL-13 induces airways hyperreactivity independently of the IL-4R alpha chain in the allergic lung. *J. Immunol.* 167:1683–92
78. Blease K, Schuh JM, Jakubzick C, Lukacs NW, Kunkel SL, et al. 2002. Stat6-deficient mice develop airway hyperresponsiveness and peribronchial fibrosis during chronic fungal asthma. *Am. J. Pathol.* 160:481–90
79. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, et al. 2002. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat. Med.* 8:885–89
80. Puri RK. 1995. Structure and function of interleukin 4 and its receptors. In *Cytokines: Interleukins and Their Receptors*, ed. R Kurzrock, M Talpaz, pp. 143–85. Norwell, MA: Kluwer
81. Blais Y, Gingras S, Haagensen DE, Labrie F, Simard J. 1996. Interleukin-4 and interleukin-13 inhibit estrogen-induced breast cancer cell proliferation and stimulate GCDFP-15 expression in human breast cancer cells. *Mol. Cell Endocrinol.* 121:11–18
82. Obiri NI, Husain SR, Debinski W, Puri RK. 1996. Interleukin 13 inhibits growth of human renal cell carcinoma cells independently of the p140 interleukin 4 receptor chain. *Clin. Cancer Res.* 2:1743–49
83. Serve H, Oelmann E, Herweg A, Oberberg D, Serve S, et al. 1996. Inhibition of proliferation and clonal growth of human breast cancer cells by interleukin 13. *Cancer Res.* 56:3583–88
84. Renard N, Duvert V, Banchereau J, Saeland S. 1994. Interleukin-13 inhibits the proliferation of normal and leukemic human B-cell precursors. *Blood* 84:2253–60
85. Kawakami K, Kawakami M, Snoy PJ, Husain SR, Puri RK. 2001. In vivo overexpression of IL-13 receptor alpha2 chain inhibits tumorigenicity of human breast and pancreatic tumors in immunodeficient mice. *J. Exp. Med.* 194:1743–54
86. Lebel-Binay S, Laguerre B, Quintin-Colonna F, Conjeaud H, Magazin M,

et al. 1995. Experimental gene therapy of cancer using tumor cells engineered to secrete interleukin-13. *Eur. J. Immunol.* 25:2340–48

87. Kobayashi M, Kobayashi H, Pollard RB, Suzuki F. 1998. A pathogenic role of Th2 cells and their cytokine products on the pulmonary metastasis of murine B16 melanoma. *J. Immunol.* 160:5869–73
88. Terabe M, Matsui S, Noben-Trauth N, Chen H, Watson C, et al. 2000. NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. *Nat. Immunol.* 1:515–20
89. Kacha AK, Fallarino F, Markiewicz MA, Gajewski TF. 2000. Cutting edge: spontaneous rejection of poorly immunogenic P1.HTR tumors by Stat6-deficient mice. *J. Immunol.* 165:6024–28
90. Ostrand-Rosenberg S, Grusby MJ, Clements VK. 2000. Cutting edge: STAT6-deficient mice have enhanced tumor immunity to primary and metastatic mammary carcinoma. *J. Immunol.* 165:6015–19
91. Chaouchi N, Wallon C, Goujard C, Tertian G, Rudent A, et al. 1996. Interleukin-13 inhibits interleukin-2-induced proliferation and protects chronic lymphocytic leukemia B cells from in vitro apoptosis. *Blood* 87:1022–29
92. Kapp U, Yeh WC, Patterson B, Elia AJ, Kagi D, et al. 1999. Interleukin 13 is secreted by and stimulates the growth of Hodgkin and Reed-Sternberg cells. *J. Exp. Med.* 189:1939–46
93. Lai YH, Mosmann TR. 1999. Mouse IL-13 enhances antibody production in vivo and acts directly on B cells in vitro to increase survival and hence antibody production. *J. Immunol.* 162:78–87
94. Billard C, Caput D, Vita N, Ferrara P, Orrico M, et al. 1997. Interleukin-13 responsiveness and interleukin-13 receptor expression in non-Hodgkin's lymphoma and reactive lymph node B cells. Modulation by CD40 activation. *Eur. Cytokine Netw.* 8:19–27
95. Skinnider BF, Elia AJ, Gascoyne RD, Trumper LH, von Bonin F, et al. 2001. Interleukin 13 and interleukin 13 receptor are frequently expressed by Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood* 97:250–55
96. Oshima Y, Puri RK. 2001. Suppression of an IL-13 autocrine growth loop in a human Hodgkin/Reed-Sternberg tumor cell line by a novel IL-13 antagonist. *Cell Immunol.* 211:37–42
97. Skinnider BF, Elia AJ, Gascoyne RD, Patterson B, Trumper L, et al. 2002. Signal transducer and activator of transcription 6 is frequently activated in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood* 99:618–26
98. Ohshima K, Akaiwa M, Umeshita R, Suzumiya J, Izuhara K, et al. 2001. Interleukin-13 and interleukin-13 receptor in Hodgkin's disease: possible autocrine mechanism and involvement in fibrosis. *Histopathology* 38:368–75
99. Debinski W, Karlsson B, Lindholm L, Siegall CB, Willingham MC, et al. 1992. Monoclonal antibody C242-Pseudomonas exotoxin A. A specific and potent immunotoxin with antitumor activity on a human colon cancer xenograft in nude mice. *J. Clin. Invest.* 90:405–11
100. Puri RK, Leland P, Obiri NI, Husain SR, Kreitman RJ, et al. 1996. Targeting of interleukin-13 receptor on human renal cell carcinoma cells by a recombinant chimeric protein composed of interleukin-13 and a truncated form of Pseudomonas exotoxin A (PE38QQR). *Blood* 87:4333–39
101. Maini A, Hillman G, Haas GP, Wang CY, Montecillo E, et al. 1997. Interleukin-13 receptors on human prostate carcinoma cell lines represent a novel target for a chimeric protein composed of IL-13 and a mutated form of Pseudomonas exotoxin. *J. Urol.* 158:948–53
102. Debinski W, Obiri NI, Powers SK, Pastan I, Puri RK. 1995. Human glioma cells overexpress receptors for interleukin 13

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and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and pseudomonas exotoxin. *Clin. Cancer Res.* 1:1253–58

103. Kornmann M, Kleeff J, Debinski W, Korc M. 1999. Pancreatic cancer cells express interleukin-13 and -4 receptors, and their growth is inhibited by Pseudomonas exotoxin coupled to interleukin-13 and -4. *Anticancer Res.* 19:125–31
104. Husain SR, Puri RK. 2000. Interleukin-13 fusion cytotoxin as a potent targeted agent for AIDS-Kaposi's sarcoma xenograft. *Blood* 95:3506–13
105. Kawakami K, Kawakami M, Joshi BH, Puri RK. 2001. Interleukin-13 receptor-targeted cancer therapy in an immunodeficient animal model of human head and neck cancer. *Cancer Res.* 61:6194–200
106. Debinski W, Miner R, Leland P, Obiri NI, Puri RK. 1996. Receptor for interleukin (IL) 13 does not interact with IL4 but receptor for IL4 interacts with IL13 on human glioma cells. *J. Biol. Chem.* 271:22428–33
107. Kawakami K, Taguchi J, Murata T, Puri RK. 2001. The interleukin-13 receptor alpha2 chain: an essential component for binding and internalization but not for interleukin-13-induced signal transduction through the STAT6 pathway. *Blood* 97:2673–79
108. Kawakami K, Husain SR, Bright RK, Puri RK. 2001. Gene transfer of interleukin 13 receptor alpha2 chain dramatically enhances the antitumor effect of IL-13 receptor-targeted cytotoxin in human prostate cancer xenografts. *Cancer Gene Ther.* 8:861–68
109. Oshima Y, Puri RK. 2001. Characterization of a powerful high affinity antagonist that inhibits biological activities of human interleukin-13. *J. Biol. Chem.* 276:15185–91
110. Debinski W, Gibo DM, Obiri NI, Kealiher A, Puri RK. 1998. Novel anti-brain tumor cytotoxins specific for cancer cells. *Nat. Biotechnol.* 16:449–53
111. Cheever AW, Williams ME, Wynn TA, Finkelman FD, Seder RA, et al. 1994. Anti-IL-4 treatment of Schistosoma mansoni-infected mice inhibits development of T cells and non-B, non-T cells expressing Th2 cytokines while decreasing egg-induced hepatic fibrosis. *J. Immunol.* 153:753–59
112. Cheever AW. 1972. Pipe-stem fibrosis of the liver. *Trans. R. Soc. Trop. Med. Hyg.* 66:947–48
113. Vella AT, Pearce EJ. 1992. $CD4^+$ Th2 response induced by *Schistosoma mansoni* eggs develops rapidly, through an early, transient, Th0-like stage. *J. Immunol.* 148:2283–88
114. Wynn TA, Eltoum I, Cheever AW, Lewis FA, Gause WC, et al. 1993. Analysis of cytokine mRNA expression during primary granuloma formation induced by eggs of *Schistosoma mansoni*. *J. Immunol.* 151:1430–40
115. Wynn TA, Cheever AW, Jankovic D, Poindexter RW, Caspar P, et al. 1995. An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. *Nature* 376:594–96
116. Cheever AW, Poindexter RW, Wynn TA. 1999. Egg laying is delayed but worm fecundity is normal in SCID mice infected with Schistosoma japonicum and S. mansoni with or without recombinant tumor necrosis factor alpha treatment. *Infect. Immun.* 67:2201–8
117. Fallon PG, Dunne DW. 1999. Tolerization of mice to Schistosoma mansoni egg antigens causes elevated type 1 and diminished type 2 cytokine responses and increased mortality in acute infection. *J. Immunol.* 162:4122–32
118. Brunet LR, Finkelman FD, Cheever AW, Kopf MA, Pearce EJ. 1997. IL-4 protects against TNF-alpha-mediated cachexia and death during acute schistosomiasis. *J. Immunol.* 159:777–85
119. Hoffmann KF, Cheever AW, Wynn TA. 2000. IL-10 and the dangers of immune polarization: excessive type 1 and type 2

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cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. *J. Immunol.* 164:6406–16

120. Pearce EJ, Cheever A, Leonard S, Covalesky M, Fernandez-Botran R, et al. 1996. Schistosoma mansoni in IL-4-deficient mice. *Int. Immunol.* 8:435–44
121. Kaplan MH, Whitfield JR, Boros DL, Grusby MJ. 1998. Th2 cells are required for the *Schistosoma mansoni* egg-induced granulomatous response. *J. Immunol.* 160:1850–56
122. Jankovic D, Kullberg MC, Noben-Trauth N, Caspar P, Ward JM, et al. 1999. Schistosome-infected IL-4 receptor knockout (KO) mice, in contrast to IL-4 KO mice, fail to develop granulomatous pathology while maintaining the same lymphokine expression profile. *J. Immunol.* 163:337–42
123. Chiaramonte MG, Donaldson DD, Cheever AW, Wynn TA. 1999. An IL-13 inhibitor blocks the development of hepatic fibrosis during a T-helper type 2-dominated inflammatory response. *J. Clin. Invest.* 104:777–85
124. Chiaramonte MG, Cheever AW, Malley JD, Donaldson DD, Wynn TA. 2001. Studies of murine schistosomiasis reveal interleukin-13 blockade as a treatment for established and progressive liver fibrosis. *Hepatology* 34:273–82
125. Fallon PG, Richardson EJ, McKenzie GJ, McKenzie AN. 2000. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. *J. Immunol.* 164:2585–91
126. Oriente A, Fedarko NS, Pacocha SE, Huang SK, Lichtenstein LM, et al. 2000. Interleukin-13 modulates collagen homeostasis in human skin and keloid fibroblasts. *J. Pharmacol. Exp. Ther.* 292:988–94
127. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, et al. 2001. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta(1). *J. Exp. Med.* 194:809–21
128. Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, et al. 2001. Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-Arginine metabolism. *J. Immunol.* 167:6533–44
129. Julia V, Hessel EM, Malherbe L, Glaichenhaus N, O'Garra A, et al. 2002. A restricted subset of dendritic cells captures airborne antigens and remains able to activate specific T cells long after antigen exposure. *Immunity* 16:271–83
130. Modolell M, Corraliza IM, Link F, Soler G, Eichmann K. 1995. Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by TH1 and TH2 cytokines. *Eur. J. Immunol.* 25:1101–4
131. Munder M, Eichmann K, Moran JM, Centeno F, Soler G, et al. 1999. Th1/Th2-regulated expression of arginase isoforms in murine macrophages and dendritic cells. *J. Immunol.* 163:3771–77
132. Hesse M, Cheever AW, Jankovic D, Wynn TA. 2000. NOS-2 mediates the protective anti-inflammatory and antifibrotic effects of the Th1-inducing adjuvant, IL-12, in a Th2 model of granulomatous disease. *Am. J. Pathol.* 157:945–55
133. Wallace WA, Ramage EA, Lamb D, Howie SE. 1995. A type 2 (Th2-like) pattern of immune response predominates in the pulmonary interstitium of patients with cryptogenic fibrosing alveolitis (CFA). *Clin. Exp. Immunol.* 101:436–41
134. Shirwan H. 1999. Chronic allograft rejection. Do the Th2 cells preferentially induced by indirect alloantigen recognition play a dominant role? *Transplantation* 68:715–26
135. Baecher-Allan CM, Barth RK. 1993. PCR analysis of cytokine induction profiles associated with mouse strain variation in

susceptibility to pulmonary fibrosis. *Reg. Immunol.* 5:207–17
136. Hasegawa M, Fujimoto M, Kikuchi K, Takehara K. 1997. Elevated serum levels of interleukin 4 (IL-4), IL-10, and IL-13 in patients with systemic sclerosis. *J. Rheumatol.* 24:328–32
137. Westermann W, Schobl R, Rieber EP, Frank KH. 1999. Th2 cells as effectors in postirradiation pulmonary damage preceding fibrosis in the rat. *Int. J. Radiat. Biol.* 75:629–38
138. Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE. 1999. The IL-4 receptor: signaling mechanisms and biologic functions. *Annu. Rev. Immunol.* 17:701–38
139. Finkelman FD, Morris SC, Orekhova T, Mori M, Donaldson D, et al. 2000. Stat6 regulation of in vivo IL-4 responses. *J. Immunol.* 164:2303–10
140. Jankovic D, Kullberg MC, Noben-Trauth N, Caspar P, Paul WE, et al. 2000. Single cell analysis reveals that IL-4 receptor/Stat6 signaling is not required for the in vivo or in vitro development of CD4+ lymphocytes with a Th2 cytokine profile. *J. Immunol.* 164:3047–55
141. Doherty TM, Kastelein R, Menon S, Andrade S, Coffman RL. 1993. Modulation of murine macrophage function by IL-13. *J. Immunol.* 151:7151–60
142. de Vries JE. 1998. The role of IL-13 and its receptor in allergy and inflammatory responses. *J. Allergy Clin. Immunol.* 102:165–69
143. Borish LC, Nelson HS, Corren J, Bensch G, Busse WW, et al. 2001. Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. *J. Allergy Clin. Immunol.* 107:963–70
144. Manetti R, Parronchi P, Giudizi MG, Piccinni MP, Maggi E, et al. 1993. Natural killer cell stimulatory factor (Interleukin 12 [IL-12]) induces T helper type 1 (Th1)-specific immune responses and inhibits the development of IL-4-producing Th cells. *J. Exp. Med.* 177:1199–204
145. Wynn TA, Jankovic D, Hieny S, Zioncheck K, Jardieu P, et al. 1995. IL-12 exacerbates rather than suppresses T helper 2-dependent pathology in the absence of endogenous IFN-gamma. *J. Immunol.* 154:3999–4009
146. Finkelman FD, Madden K, Cheever A, Katona IM, Morris SC, et al. 1994. Effects of interleukin-12 on immune responses and host protection in mice infected with intestinal nematode parasites. *J. Exp. Med.* 179:1563–72
147. Gavett SH, O'Hearn DJ, Li X, Huang SK, Finkelman FD, et al. 1995. Interleukin 12 inhibits antigen-induced airway hyperresponsiveness, inflammation, and Th2 cytokine expression in mice. *J. Exp. Med.* 182:1527–36
148. Kline JN, Waldschmidt TJ, Businga TR, Lemish JE, Weinstock JV, et al. 1998. Modulation of airway inflammation by CpG oligodeoxynucleotides in a murine model of asthma. *J. Immunol.* 160:2555–59
149. Sur S, Wild JS, Choudhury BK, Sur N, Alam R, et al. 1999. Long term prevention of allergic lung inflammation in a mouse model of asthma by CpG oligodeoxynucleotides. *J. Immunol.* 162:6284–93
150. Krieg AM. 1999. CpG DNA: a novel immunomodulator. *Trends Microbiol.* 7:64–65
151. Ford JG, Rennick D, Donaldson DD, Venkayya R, McArthur C, et al. 2001. Il-13 and IFN-gamma: interactions in lung inflammation. *J. Immunol.* 167:1769–77
152. Okamura H, Tsutsi H, Komatsu T, Yutsudo M, Hakura A, et al. 1995. Cloning of a new cytokine that induces IFN-gamma production by T cells. *Nature* 378:88–91
153. Hofstra CL, Van Ark I, Hofman G, Kool M, Nijkamp FP, et al. 1998. Prevention of Th2-like cell responses by coadministration of IL-12 and IL-18 is associated with inhibition of antigen-induced airway hyperresponsiveness, eosinophilia, and serum IgE levels. *J. Immunol.* 161:5054–60

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154. Kodama T, Matsuyama T, Kuribayashi K, Nishioka Y, Sugita M, et al. 2000. IL-18 deficiency selectively enhances allergen-induced eosinophilia in mice. *J. Allergy Clin. Immunol.* 105:45–53
155. Walter DM, Wong CP, DeKruyff RH, Berry GJ, Levy S, et al. 2001. Il-18 gene transfer by adenovirus prevents the development of and reverses established allergen-induced airway hyperreactivity. *J. Immunol.* 166:6392–98
156. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. 2001. Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. *Cytokine Growth Factor Rev.* 12:53–72
157. Yoshimoto T, Tsutsui H, Tominaga K, Hoshino K, Okamura H, et al. 1999. IL-18, although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc. Natl. Acad. Sci. USA* 96:13962–66
158. Yoshimoto T, Mizutani H, Tsutsui H, Noben-Trauth N, Yamanaka K, et al. 2000. IL-18 induction of IgE: dependence on CD4+ T cells, IL-4 and STAT6. *Nat. Immunol.* 1:132–37
159. Wild JS, Sigounas A, Sur N, Siddiqui MS, Alam R, et al. 2000. IFN-gamma-inducing factor (IL-18) increases allergic sensitization, serum IgE, Th2 cytokines, and airway eosinophilia in a mouse model of allergic asthma. *J. Immunol.* 164:2701–10
160. Kumano K, Nakao A, Nakajima H, Hayashi F, Kurimoto M, et al. 1999. Interleukin-18 enhances antigen-induced eosinophil recruitment into the mouse airways. *Am. J. Respir. Crit. Care Med.* 160:873–78
161. Helmby H, Takeda K, Akira S, Grencis RK. 2001. Interleukin (IL)-18 promotes the development of chronic gastrointestinal helminth infection by downregulating IL-13. *J. Exp. Med.* 194:355–64
162. Hoffmann KF, Caspar P, Cheever AW, Wynn TA. 1998. IFN-γ, IL-12, and TNF-α are required to maintain reduced liver pathology in mice vaccinated with Schistosoma mansoni eggs and IL-12. *J. Immunol.* 161:4201–10
163. Henri S, Chevillard C, Mergani A, Paris P, Gaudart J, et al. 2002. Cytokine regulation of periportal fibrosis in humans infected with schistosoma mansoni: IFN-gamma is associated with protection against fibrosis and TNF-alpha with aggravation of disease. *J. Immunol.* 169:929–36
164. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. 2001. Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol.* 19:683–765
165. Grunig G, Corry DB, Leach MW, Seymour BW, Kurup VP, et al. 1997. Interleukin-10 is a natural suppressor of cytokine production and inflammation in a murine model of allergic bronchopulmonary aspergillosis. *J. Exp. Med.* 185:1089–99
166. Wynn TA, Morawetz R, Scharton-Kersten T, Hieny S, Morse H, et al. 1997. Analysis of granuloma formation in double cytokine-deficient mice reveals a central role for IL-10 in polarizing both T helper cell 1- and T helper cell 2-type cytokine responses in vivo. *J. Immunol.* 159:5014–23
167. Wynn TA, Cheever AW, Williams ME, Hieny S, Caspar P, et al. 1998. IL-10 regulates liver pathology in acute murine schistosomiasis mansoni but is not required for immune down-modulation of chronic disease. *J. Immunol.* 160: 5000–8
168. Vaillant B, Chiaramonte MG, Cheever AW, Soloway PD, Wynn TA. 2001. Regulation of hepatic fibrosis and extracellular matrix genes by the Th response: new insight into the role of tissue inhibitors of matrix metalloproteinases. *J. Immunol.* 167:7017–26
169. Stampfli MR, Cwiartka M, Gajewska BU, Alvarez D, Ritz SA, et al. 1999. Interleukin-10 gene transfer to the airway regulates allergic mucosal sensitization

Annu. Rev. Immunol. 2003.21:425-456. Downloaded from www.annualreviews.org
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in mice. *Am. J. Respir. Cell Mol. Biol.* 21:586–96
170. Umetsu DT, DeKruyff RH. 1999. Interleukin-10: the missing link in asthma regulation? *Am. J. Respir. Cell Mol. Biol.* 21:562–63
171. Wills-Karp M, Santeliz J, Karp CL. 2001. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat. Rev. Immunol.* 1:69–75
172. Yazdanbakhsh M, Kremsner PG, van Ree R. 2002. Allergy, parasites, and the hygiene hypothesis. *Science* 296:490–94
173. van den Biggelaar AHJ, van Ree R, Rodrigues LC, Lell B, Deelder AM, et al. 2000. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. *Lancet* 356:1723–27
174. Tournoy KG, Kips JC, Pauwels RA. 2000. Endogenous interleukin-10 suppresses allergen-induced airway inflammation and nonspecific airway responsiveness. *Clin. Exp. Allergy* 30:775–83
175. Akbari O, DeKruyff RH, Umetsu DT. 2001. Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. *Nat. Immunol.* 2:725–31
176. Zuany-Amorim C, Sawicka E, Manlius C, Le Moine A, Brunet LR, et al. 2002. Suppression of airway eosinophilia by killed Mycobacterium vaccae-induced allergen-specific regulatory T-cells. *Nat. Med.* 8:625–29
177. Makela MJ, Kanehiro A, Borish L, Dakhama A, Loader J, et al. 2000. IL-10 is necessary for the expression of airway hyperresponsiveness but not pulmonary inflammation after allergic sensitization. *Proc. Natl. Acad. Sci. USA* 97:6007–12
178. Justice JP, Shibata Y, Sur S, Mustafa J, Fan M, et al. 2001. IL-10 gene knockout attenuates allergen-induced airway hyperresponsiveness in C57BL/6 mice. *Am. J. Physiol. Lung Cell Mol. Physiol.* 280:L363–68
179. Yang X, Wang S, Fan Y, Han X. 2000. IL-10 deficiency prevents IL-5 overproduction and eosinophilic inflammation in a murine model of asthma-like reaction. *Eur. J. Immunol.* 30:382–91
180. Fallon PG, Richardson EJ, McKenzie GJ, McKenzie AN. 2000. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. *J. Immunol.* 164:2585–91
181. Oriente A, Fedarko NS, Pacocha SE, Huang SK, Lichtenstein LM, et al. 2000. Interleukin-13 modulates collagen homeostasis in human skin and keloid fibroblasts. *Pharmacol. Exp. Ther.* 292:988–94
182. Booth BW, Adler KB, Bonner JC, Tournier F, Martin LD. 2001. Interleukin-13 induces proliferation of human airway epithelial cells in vitro via a mechanism mediated by transforming growth factor-alpha. *Am. J. Respir. Cell Mol. Biol.* 25:739–43
183. Aman MJ, Tayebi N, Obiri NI, Puri RK, Modi WS, et al. 1996. cDNA cloning and characterization of the human interleukin 13 receptor alpha chain. *J. Biol. Chem.* 271:29265–70
184. Caput D, Laurent P, Kaghad M, Lelias JM, Lefort S, et al. 1996. Cloning and characterization of a specific interleukin (IL)-13 binding protein structurally related to the IL-5 receptor alpha chain. *J. Biol. Chem.* 271:16921–26
185. Hilton DJ, Zhang JG, Metcalf D, Alexander WS, Nicola NA, et al. 1996. Cloning and characterization of a binding subunit of the interleukin 13 receptor that is also a component of the interleukin 4 receptor. *Proc. Natl. Acad. Sci. USA* 93:497–501
186. Zurawski SM, Vega F Jr, Huyghe B, Zurawski G. 1993. Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction. *EMBO J.* 12:2663–70
187. Zhang JG, Hilton DJ, Willson TA, McFarlane C, Roberts BA, et al. 1997. Identification, purification, and characterization

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of a soluble interleukin (IL)-13-binding protein. Evidence that it is distinct from the cloned Il-13 receptor and Il-4 receptor alpha-chains. *J. Biol. Chem.* 272:9474–80

188. Colotta F, Re F, Muzio M, Bertini R, Polentarutti N, et al. 1993. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science* 261:472–75
189. Abbas AK, Murphy KM, Sher A. 1996. Functional diversity of helper T lymphocytes. *Nature* 383:787–93

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