

Molecular mechanisms in allergy and clinical immunology

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The other side of the coin: The protective role of the T_H2 cytokines

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Although T_H2 cytokine involvement in allergy makes these cytokines attractive therapeutic targets, they protect against ectoparasites and gastrointestinal worms and suppress inflammation induced by T_H1 cytokines. T_H2 cytokines induce mastocytosis, eosinophilia, IgE synthesis, and mucus production. Each element of this response protects against some worms; however, different worms are protected against by different elements of the total response. The induction of the entire response by most parasitic worms suggests that it is safer for the immune system to make a stereotyped worm-protective response than to attempt to match a more specific response to a particular worm. In contrast, the reciprocal antagonism between T_H1 and T_H2 cytokines suggests that it is safer for the immune system to limit immunopathology by suppressing inflammatory effector mechanisms not required for host protection against a particular pathogen class than to make an all-purpose inflammatory response. This, in turn, implies that innate immunity can distinguish different classes of parasites (eg, worms vs protozoa) but has limited ability to distinguish individual parasites within a class (eg, different worms). Although these considerations suggest that T_H2 cytokine antagonists may increase the risk and severity of worm infections and T_H1 cytokine-mediated inflammatory disorders, such therapy should be relatively safe if it is restricted to areas in which worm infections are rare and commonsense precautions are taken to minimize the risk of inducing T_H1 cytokine-related inflammatory disease. (J Allergy Clin Immunol 2001;107:772-80.)

Key words: Allergy, eosinophil, IgE, IL-3, IL-4, IL-5, IL-9, IL-13, mast cell, worm

Study of the roles played by cytokines in disease has been a priority for immunologists, particularly since

Abbreviation used
IL-4R α : IL-4 receptor α chain

Mosmann et al¹ discovered that fully differentiated mouse CD4⁺ T cells tend to secrete one of 2 different sets of cytokines and Heinzel et al² and Scott et al³ discovered that infection with an intracellular protozoan parasite, *Leishmania major*, resolves in mice that produce one cytokine set (T_H1) but is exacerbated in mice that produce the other set (T_H2). The initial description of these 2 cytokine sets identified IFN- γ and IL-2 as T_H1 cytokines and IL-4 as a T_H2 cytokine. Subsequent studies have identified additional members of each cytokine set (lymphotoxin in the T_H1 set and IL-5, IL-9, and IL-13 in the T_H2 set)⁴⁻⁷ and have established IFN- γ and IL-4 as the prototypic T_H1 and T_H2 cytokines, respectively, which, in addition to important effects on many cell types, promote the differentiation of naive T cells into effector T_H1 or T_H2 cells.^{5,8-11}

As studies of cytokine biology advanced, it became apparent that the T_H2 cytokines (and an *honorary* T_H2 cytokine, IL-3, which is produced by T_H1 and T_H2 cells) all have effects that are associated with atopy and asthma (Table I), whereas IFN- γ , IFN- α , IFN- β , and IL-12, a cytokine made predominantly by antigen-presenting cells, all suppress these effects directly and suppress the differentiation of naive T cells into T_H2 cells.¹¹⁻²¹ To some extent, these initial observations created a mind set that regarded T_H1 cytokines as the *good* cytokines that inhibit immunopathology and control infection and T_H2 cytokines as the *bad* cytokines that promote immunopathology and exacerbate infection.²² Some investigators suggested that regulation of worm infections might be a likely exception to this paradigm because (1) worm infections are associated with vigorous and selective production of T_H2 cytokines and the allergic immunophenomena that are induced by these cytokines; (2) a good theoretical case could be made that allergy-associated molecules and cells, including IgE, mucus, and mast cells, might promote worm expulsion; and (3) eosinophils can kill larval forms of schistosome parasites *in vitro*.²³⁻²⁶ In opposition to this view, studies of a mouse vaccine model of schistosomiasis produced clear evidence for IFN- γ -mediated immunity and T_H2

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cytokine-mediated immunopathology.²⁷⁻³¹ Furthermore, initial investigations of mice infected with the gastrointestinal nematode *Trichinella spiralis* indicated that a mouse strain whose spleen cells made a predominantly T_H1 cytokine response expelled worms more rapidly than a strain whose spleen cells made more of a T_H2 response.²²

This review will defend a view that the goodness or badness of a particular cytokine response is situation dependent: either T_H1 or T_H2 cytokines can promote protective immunity or exacerbate infection, depending on the pathogen involved, and the effector mechanisms through which a T_H1 or T_H2 cytokine response defends against infection are the same processes that cause inflammatory disease when induced inappropriately or in an exaggerated form. Through discussion of cytokine effects on the resolution of gastrointestinal worm infections and studies of T_H1 cytokine-associated inflammatory disease, we will argue that the T_H2 cytokine response is required both for host protection against a class of parasites and for suppression of T_H1 cytokine-induced immunopathology. We will also argue that the combination of T_H2 cytokine-induced inflammatory processes that typifies atopy and asthma is the precise combination that has evolved to defend against the panoply of gastrointestinal nematode parasites and is induced by many such parasites, even though different elements of the total response defend against different parasites.

CYTOKINE REGULATION OF HOST PROTECTION AGAINST GASTROINTESTINAL NEMATODE PARASITES

Studies of 2 nematode parasites that invade the host by means of oral ingestion and reside solely in the gut provided the initial strong evidence that T_H2 cytokines are host protective. Experiments in which mice were given a primary or a second infection with *Heligmosomoides polygyrus* demonstrated that the primary infection is long lasting and relatively severe, whereas second infections tend to be much less severe.³² Treating previously infected mice with a neutralizing antibody to IL-4 or with a blocking antibody to the IL-4 receptor α chain (IL-4R α) totally eliminated the protective effects of a previous infection.³³ Experiments in which mice were given a primary infection with the whipworm, *Trichuris muris* (a close relative of *Trichuris trichiura*, which causes human disease) demonstrated that some mouse strains expelled the parasite before it could mature into an egg-laying adult, whereas other strains had a chronic infection. Resistant strains made a T_H2 cytokine response to infection, whereas susceptible strains made a T_H1 cytokine response.³⁴ Furthermore, treatment of susceptible strains with anti-IFN- γ antibody or with a long-acting formulation of IL-4 made them resistant to infection, whereas treatment of resistant strains with anti-IL-4R α mAb or IL-12, which induces IFN- γ production and suppresses the T_H2 cytokine response, made them highly susceptible.³⁵ These latter observations are exactly opposite to those made in mice infected with the intracellular proto-

TABLE I. Involvement of T_H2 cytokines in allergy and asthma*

Stimulation of IgE production	IL-4, IL-9, IL-13†
Eosinophil, neutrophil, and mast cell infiltrates	IL-4, IL-5, IL-9, IL-13
Mastocytosis	IL-3,‡ IL-4, IL-9
Goblet cell hyperplasia	IL-4, IL-5, IL-9, IL-13
T _H 2 cell differentiation	IL-4
Increased adhesion molecule expression	IL-4, IL-13
Increased vascular permeability	IL-4, IL-5, IL-13
Airway hyperresponsiveness	IL-4?, IL-5, IL-9, IL-13
Smooth muscle hyperplasia	IL-4, IL-9, IL-13
Subepithelial fibrosis	IL-4, IL-5, IL-9, IL-13

*Additional cytokines, including IL-1, IL-6, IL-11, TNF- α , and several chemokines have also been implicated in allergy and asthma.

†IL-13 stimulates IgE responses in human patients but probably not in mice.

‡IL-3 is made by T_H1 and T_H2 cells (as is IL-13 in human patients) but has an important role in induction of mastocytosis.

zoan parasite *Leishmania major* and thus demonstrate that the immunoprotective effects of a cytokine are parasite specific.

Additional studies have examined whether the IL-4R α chain is required for host protection against other gastrointestinal nematode parasites, including *Trichinella spiralis*, *Nippostrongylus brasiliensis*, and *Strongyloides venezuelensis*. Although these different worms are not all expelled by the same effector mechanisms (see below), expulsion is prevented or greatly retarded in each case in anti-IL-4R α antibody-treated mice or in mice that lack a functional IL-4R α gene.³⁶⁻³⁹ Thus IL-4R α -mediated signaling appears to be a consistent requirement for host protection against gastrointestinal nematode parasites.

IL-4 is not as consistently required as IL-4R α for host protection against gastrointestinal nematodes. For example, worm expulsion is normal in IL-4-deficient mice infected with *Nippostrongylus brasiliensis* or *Trichinella spiralis* and in some strains of mice infected with *Trichuris muris*.^{36-38,40} This observation is explained by a second T_H2 cytokine, IL-13, that binds to a receptor that includes IL-4R α . IL-4R α can pair with either of 2 chains, cytokine receptor common γ chain (a constituent of the IL-2, IL-4, IL-9, and IL-15 receptors) or IL-13 receptor α_1 chain, to form the type 1 and type 2 IL-4 receptors, respectively.⁴¹ The type 1 IL-4 receptor, which binds and is activated by IL-4 but not IL-13, is the only IL-4 receptor on T cells and is generally expressed by cells of the immune system but is not present on several nonimmune cell types. However, the type 2 IL-4 receptor, which binds and is activated by both IL-4 and IL-13, is present on smooth muscle cells, gut and lung epithelial cells, and some cells of the immune system (macrophages and human, but not mouse, B cells). The relative roles of IL-4 and IL-13 in gastrointestinal worm expulsion vary among worm infections and mouse strains. For example, studies with an IL-13 antagonist and in IL-13-deficient mice demonstrate that IL-13 is more involved than IL-4 in the expulsion of *Nip-*

TABLE II. Cytokine and signaling molecule promotion of host protection against nematodes*

Worm	Promoter of host protection
<i>Trichinella spiralis</i>	c-kit ligand, IL-3, IL-4, IL-13, IL-4R α , Stat6
<i>Nippostrongylus brasiliensis</i>	IL-4, IL-5, [†] IL-13, [‡] IL-4R α , Stat6
<i>Heligmosomoides polygyrus</i>	IL-4, IL-4R, Stat6
<i>Trichuris muris</i> [§]	IL-4, IL-9, IL-13, TNF- α , IL-4R, Stat6
<i>Onchocerca volvulus</i>	IL-5
<i>Strongyloides</i> species [#]	c-kit ligand, IL-3, IL-4, IL-5, Stat6
<i>Angiostrongylus cantonensis</i>	IL-5
<i>Litomosoides sigmodontis</i>	IL-5

*Some of the associations shown here are probably more general than indicated because studies in some worm species have been limited. IL-4R α and Stat6 may be required for protection against all gastrointestinal worms.

[†]Only demonstrated in transgenic mice that overexpress IL-5.

[‡]IL-13 is more important than IL-4 in protecting mice against this parasite.

[§]Cytokine requirements for host protection vary among different mouse strains.

[#]Includes *Strongyloides ratti*, *Strongyloides stercoralis*, and *Strongyloides venezuelensis*.

postrongylus brasiliensis,³⁶ whereas either IL-4 or IL-13 suffices to expel *Trichinella spiralis*,³⁷ and both IL-4 and IL-13 are required for some mouse strains to expel *Trichuris muris*.^{39,40} Studies with *Trichuris muris* in different mouse strains are particularly revealing. BALB/c mice, which appear to be genetically predisposed to mount a strong T_H2 response, expel *Trichuris muris*, even in the absence of IL-4, most likely because they still make sufficient IL-13 to induce expulsion. In contrast, C57BL/6 mice, which tend to be T_H1 biased, fail to expel *Trichuris muris* in the absence of IL-4. Treatment of *Trichuris muris*-infected C57BL/6 mice with anti-IFN- γ antibody allows expulsion in the absence of either IL-4 or IL-13, but not both.³⁹ These observations and the observation that treatment with exogenous IL-4 induces *Nippostrongylus brasiliensis* expulsion by IL-13-deficient mice (Schopf L, Urban JF Jr, Finkelman FD, unpublished data) suggest that IL-4 and IL-13 may induce worm expulsion through the same mechanisms and that differences in the importance of these 2 cytokines in the expulsion of a particular parasite may depend on the relative amounts of these cytokines produced in a particular infection and on the relative stability of these cytokines and their relative potencies in triggering IL4R α -mediated signaling on cell types relevant to expulsion.

IL-4 and IL-13 are not the only T_H2 cytokines that can contribute to gastrointestinal worm expulsion, but they are the only cytokines for which a consistent requirement has been demonstrated. IL-9 is required for expulsion of *Trichuris muris*, at least in C57BL/6 mice,⁴² and mice that overexpress IL-9 demonstrate rapid expulsion of this parasite.⁴³ These observations may reflect the ability of IL-9 to enhance IL-4R α -related inflammatory responses,

particularly when IL-4 is limiting. IL-5 does not appear to have a consistent role in the expulsion of adult worms but promotes the destruction of larval forms of some worms as they migrate through the body. IL-3 does not contribute to host protection against *Nippostrongylus brasiliensis* but does contribute to the expulsion of *Strongyloides* species and *Trichinella spiralis*, presumably by stimulating mastocytosis. Cytokine contributions to host protection against gastrointestinal worms are summarized in Table II.

EFFECTOR MECHANISMS INVOLVED IN GASTROINTESTINAL WORM EXPULSION

The observation that the IL-4R α -activated signaling molecule Stat6 appears to be a universal requirement for gastrointestinal worm expulsion (Urban JF Jr, Finkelman FD, unpublished observations)^{36,37} might suggest that a single effector mechanism underlies expulsion of all gastrointestinal worms. Surprisingly, Stat6 signaling appears to contribute to the expulsion of different worms in different ways. Stat6 signaling is essential for IL-4 enhancement of T_H2 cytokine production.⁴⁴⁻⁴⁶ Consequently, the absence of Stat6 causes a decrease in IL-3 and IL-4 production and an increase in IFN- γ production in *Trichinella spiralis*-infected mice.³⁷ Because mast cell responses, which are required for *Trichinella spiralis* expulsion,^{37,47-53} are stimulated by IL-3 and IL-4⁵⁴ and inhibited by IFN- γ ,¹² this shift in cytokine production suppresses the normal mast cell response to this parasite and prevents parasite expulsion.³⁷ Correcting this imbalance by administering IL-4 to *Trichinella spiralis*-infected Stat6-deficient mice restores mastocytosis and enhances, but does not normalize, parasite expulsion.³⁷ In contrast, Stat6-deficient mice infected with *Nippostrongylus brasiliensis* mount a normal T_H2 cytokine response and an increased mast cell response but still fail to expel the parasite.³⁶ Administration of exogenous IL-4 or IL-13 to these mice has no effect on *Nippostrongylus brasiliensis* expulsion, even though IL-4 treatment induces T cell-deficient mice to expel this parasite.⁵⁵ Thus in *Trichinella spiralis*-infected mice, Stat6 signaling seems to indirectly promote worm expulsion by stimulating production of the cytokines that directly induce a critical, mast cell-related effector mechanism, whereas in *Nippostrongylus brasiliensis*-infected mice Stat6 signaling more directly induces still unidentified effector mechanisms that promote expulsion. Recent experiments with chimeric mice produced by reconstituting irradiated IL-4R α -deficient mice with normal bone marrow or irradiated IL-4R α -sufficient mice with IL-4R α -deficient bone marrow reinforce the latter conclusion but qualify the former one. *Nippostrongylus brasiliensis* is expelled normally by mice whose lymphoid cells lack IL-4R α and fail to secrete IgE, provided that their intestinal cells are IL-4 and IL-13 responsive. However, this parasite is not expelled by mice whose lymphoid cells express IL-4R α if their intestinal cells lack this receptor, even though these mice make normal IgE, eosinophil, and mast cell

responses. The situation with *Trichinella spiralis* is more complex. IL-4R α expression by both lymphoid and intestinal cells is required for optimal worm expulsion, even though mast cell responses are normal in mice with normal bone marrow–derived cells and IL-4R α –deficient intestinal cells.⁵⁶ This result may be explained by a recent observation that IL-4 and IL-13 greatly sensitize some organs to the effects of mast cell–produced mediators, such as histamine and platelet-activating factor.⁵⁷

The involvement of mast cells in the expulsion of some, but not all, gastrointestinal nematodes has been demonstrated predominantly in experiments in which the development of mastocytosis is inhibited by a genetic deficiency in c-kit or c-kit ligand or neutralization of the latter with an mAb. These studies have demonstrated that c-kit and c-kit ligand are involved in the expulsion of *Strongyloides venezuelensis* and *Trichinella spiralis*, suggesting that mast cells are required for normal expulsion.^{48,50,51,53,58,59} This interpretation is supported by experiments in which normal expulsion of these parasites was reconstituted by infusion of normal bone marrow–derived mast cells and by experiments that demonstrated that the mast cell products, histamine, serotonin, and mouse mast cell protease 1 are involved in the expulsion of *Trichinella spiralis*.^{52,60–62}

Although mast cell degranulation is stimulated by antigen cross-linking of antigen-specific IgE bound to the high-affinity IgE receptor Fc ϵ RI on mast cells and basophils, IgE and even B cells are not required for mast cell–dependent worm expulsion. During a primary infection, *Trichinella spiralis* is expelled normally in B cell–deficient mice but is not expelled in mast cell–deficient mice.³⁷ In contrast, B cells in general and IgE in particular appear to contribute to the accelerated worm expulsion that occurs during a challenge infection. Worm expulsion is retarded during a second *Trichinella spiralis* infection in IL-4–deficient mice, Fc receptor γ chain–deficient mice (which lack Fc ϵ RI and Fc γ receptor III), and most likely in Fc ϵ RI α –deficient mice (which selectively lack Fc ϵ RI).⁶³ Most likely, insufficient high-affinity, antigen-specific antibody is produced early enough during a primary infection to supercede antibody-independent triggers of mast cell degranulation, whereas the high-affinity, high-titer antibody responses that are characteristic of a challenge infection allow mast cells to be triggered more rapidly.

In contrast to results observed with *Trichinella spiralis* and *Strongyloides venezuelensis*, expulsion of *Nippostrongylus brasiliensis* or *Trichuris muris* remains normal in mast cell–deficient mice.^{54,64–68} Effector mechanisms responsible for the expulsion of these 2 parasites have been much more difficult to identify. Although IL-4 and IL-13 have been shown to induce changes in intestinal and vascular permeability, fluid secretion and absorption, smooth muscle contractility, and mucus production that may well contribute to the expulsion of these parasites,^{38,69–73} it has not, up to now, been possible to selectively eliminate or block any of these putative effects without blocking IL-4/IL-13 production or signaling. Technical advances that allow or prevent IL-4R α expression or Stat6 expression by a single cell type should facilitate identification of the cell

type or types critical for worm expulsion and, by this means, focus attention on the most likely defense mechanisms.

Attempts to identify the role of eosinophils in gastrointestinal worm expulsion have generally used IL-5–deficient mice, which have few eosinophils or have depleted eosinophils, or have treated normal mice with anti-IL-5 antibody. Neutralization or absence of IL-5 has failed to alter the expulsion of the nematode parasites *Nippostrongylus brasiliensis*, *Heligmosomoides polygyrus*, *Trichuris muris*, *Trichinella spiralis*, and *Toxocara canis*; the cestodes *Mesocostoides corti* and *Hymenolepis diminuta*; and the trematode *Fasciola hepatica*^{38,74,75} but has increased numbers of adult *Strongyloides ratti* and *Strongyloides venezuelensis* in mouse intestines, probably by blocking eosinophil killing of larvae as they migrate from the lungs of infected mice to their intestines.^{76,77} It has also increased the survival of larval forms of *Strongyloides stercoralis* and *Angiostrongylus cantonensis*^{78–80} and the filarial parasite *Onchocerca lienalis*.⁸¹ In addition, increased expression of IL-5 has been associated with increased killing of larval forms of *Nippostrongylus brasiliensis* and adult *Litomosoides sigmodontis*, a filarial worm that resides in the lungs.^{82,83} The most likely interpretation of these observations is that IL-5, through its stimulatory effects on eosinophilopoiesis, eosinophil survival, eosinophil migration, and eosinophil activation, can promote eosinophil killing of worm larvae as they migrate through body tissues but has little effect on adult worms, unless they reside in solid tissue rather than the gut lumen. Two caveats to this conclusion are that (1) IL-5 has stimulatory effects on cells other than eosinophils, including mast cells (increased production of leukotrienes),⁸⁴ B1 B cells (increased proliferation and antibody production),⁸⁵ and nerve cells,⁸⁶ and (2) even though eosinophil numbers are greatly decreased in the blood of IL-5–deficient or anti-IL-5 antibody-treated mice, substantial numbers of eosinophils can still be found in the intestines of these mice.⁸⁷ Thus it is impossible to be absolutely certain that defects in worm killing in IL-5–deficient or anti-IL-5 antibody-treated mice are eosinophil related or that the normal survival of adult worms in these mice indicates that eosinophils are not involved in the killing of adult worms.

In summary, mast cells that are stimulated by IL-3, IL-4, and IL-9 are important for the expulsion of some but not all gastrointestinal worms, eosinophils that are stimulated by IL-5 probably contribute to the killing of worm larvae, and increases in intestinal mucus production, epithelial permeability and secretion, and smooth muscle contractility that are stimulated by IL-4, IL-13, or both may contribute to the expulsion of adult worms (Table III).

PROTECTIVE ROLE OF T_H2 CYTOKINES IN NONHELMINTHIC INFECTIONS

In addition to providing protection against helminthic parasites, T_H2 cytokines probably protect against some ectoparasites, such as the tick, *Haemaphysalis longicornis*.

TABLE III. Contributions of allergy-related immune effector mechanisms to host protection*

Effector	Protects against
Eosinophils	<i>Angiostrongylus cantonensis</i> larvae <i>Strongyloides</i> larvae <i>Onchocerca volvulus</i> larvae <i>Nippostrongylus brasiliensis</i> larvae [†]
Mucus	<i>Nippostrongylus brasiliensis</i>
IgE	<i>Trichinella spiralis</i> (2° infection) <i>Haemaphysalis longicornis</i> <i>Schistosoma mansoni</i> (human infections) <i>Strongyloides stercoralis</i> (human infections)
Mast cells	<i>Trichinella spiralis</i> <i>Strongyloides</i> species
Smooth muscle hyperresponsiveness	<i>Nippostrongylus brasiliensis</i>
Increased intestinal permeability	<i>Nippostrongylus brasiliensis</i>
Cytokine/mediator synergy	<i>Trichinella spiralis</i>

*Species for which the strongest evidence exists are shown in bold type. Regular type implies a correlation rather than any evidence of a causal relationship. In all cases the role of an effector mechanism is difficult to distinguish from the role of cytokines that promote that mechanism.

[†]Shown for *Nippostrongylus brasiliensis* only in transgenic mice that overexpress IL-5.

nis. Protection appears to involve mast cells and IgE.⁸⁸ Most likely, tick-induced mast cell degranulation increases vascular permeability, causing sufficient skin edema to prevent the tick from locating a host blood vessel. Because mast cells appear to have a general role in the initiation of inflammation⁸⁹ and mast cell deficiency is associated with increased susceptibility to bacterial infections,⁹⁰ it is possible that T_H2 cytokine induction of mastocytosis may contribute to host protection against a broad spectrum of pathogens.

Additional evidence that T_H2 cytokines may have a general role in host protection comes from studies with transgenic mice that overexpress a T_H2 cytokine; for example, mice that selectively overexpress IL-4 in their lungs demonstrate increased resistance to pulmonary infection with *Pseudomonas aeruginosa*.⁹¹ Increased bacterial susceptibility of mice deficient in a T_H2 cytokine has not, however, been clearly demonstrated.

ANTI-INFLAMMATORY ROLE OF T_H2 CYTOKINES

IL-4 and IL-13 have been referred to as anti-inflammatory cytokines, despite their prominent role in allergic inflammation, because they can suppress inflammatory responses that are associated with T_H1 cytokine production. Some of these anti-inflammatory effects result from suppression of production of IL-1, IL-12, TNF- α , and IFN- γ , which induce precursor T cells to differentiate into cytotoxic T lymphocytes that kill targets through a contact-dependent mechanism. Additional anti-inflam-

matory effects result from suppression of macrophage responsiveness to IFN- γ and TNF- α .⁹²⁻⁹⁶ These effects of IL-4 and IL-13 decrease the activity of enzymes, such as nitric oxide synthase II, which produces reactive nitrogen intermediates that macrophages use to kill ingested pathogens.^{95,96} The importance of the anti-inflammatory effects of IL-4 is illustrated by the increased inflammation and death observed in IL-4-deficient mice infected with some pathogens, such as *Schistosoma mansoni*⁹⁷ or *Borrelia burgdorferi* (the bacterium responsible for Lyme disease).^{98,99}

Equally important evidence that T_H2 cytokines can protect against inflammatory disease comes from studies of the nonobese diabetic mouse model of type 1 diabetes mellitus and the experimental allergic encephalitis model of multiple sclerosis. Pancreatic islet lesions in the former model and central nervous system lesions in the latter contain T-cell infiltrates that produce predominantly T_H1 cytokines.¹⁰⁰⁻¹⁰² Importantly, both diseases can be prevented by treating mice with IL-4.^{103,104} Thus just as an imbalance toward T_H2 cytokine production may be responsible for allergic disease, insufficient T_H2 cytokine production may predispose to other inflammatory disorders.

EVOLUTIONARY CONSIDERATIONS

The observations discussed up to this point raise 2 related philosophical questions. First, why should there be 2 separate sets of cytokines that induce effector mechanisms directed against different sets of pathogens rather than a single all-purpose set of cytokines that induces all pathogen-responsive effector mechanisms? This would prevent pathogens from evading the immune system by evolving mechanisms to induce the wrong cytokine response. Second, why should the immune system make the same stereotyped cytokine and inflammatory response to most helminthic parasites, even though that response contains elements that may damage the host but provide no protection against a particular parasite (eg, the mast cell response to *Nippostrongylus brasiliensis*)?

We believe that the answer to the first question reflects the ability of the host to distinguish between general classes of pathogens by recognizing characteristics common to a pathogen class (eg, gram-negative bacterial LPS and viral double-stranded mRNA). Recognition of such pathogen class-specific characteristics by receptors on phagocytes and antigen-presenting cells, such as the toll receptors,^{105,106} causes these cells to produce cytokines that direct an inflammatory and immune response that will likely kill or contain the invading pathogen and suppress types of inflammation that are more likely to damage the host than to protect the host against the pathogen.

The second question is more difficult to answer. The existence of a stereotyped response to nematode parasites suggests that hosts are unable to distinguish features of the different parasites within this class with sufficient reliability to allow them to make a more circumscribed response. Perhaps the putative pattern recognition receptors that identify *worminess* bind molecules common to all or most

worms; if so, it would be safest for the host to make a global response that protects against most worms by activating all effector mechanisms that have antihelminthic effects. This argument might suggest that hosts have been unable to evolve receptors for worm molecules that correlate with a worm's susceptibility to a particular host defense mechanism, if indeed such correlations exist, and that non-helminth molecules may bind to worminess receptors. Such molecules (allergens) would trigger the stereotyped antihelminth (T_H2 cytokine) response, even though they were no threat to the host. It needs pointing out that this hypothesis is highly speculative; no receptors that specifically induce a T_H2 cytokine response have been identified, and alternate answers to the second question are feasible. For example, environmental conditions that favor infection with one gastrointestinal worm species also favor infection with other species of worms. If infected hosts are likely to simultaneously harbor several worm species, perhaps it makes sense for the host to respond to the most immunogenic of the parasites by activating defense mechanisms that will eliminate all worms.

RELEVANCE TO HUMAN PATIENTS

Although there is no direct evidence that T_H2 cytokines or T_H2 cytokine-associated immune responses protect against worm infection in human patients, clinical observations are consistent with the results of rodent studies. As in rodents, human worm infections are generally associated with T_H2 cytokine responses, eosinophilia, mastocytosis, and high levels of serum IgE.¹⁰⁷ Studies of patients living in endemic areas who have been cured of *Schistosoma mansoni* infection reveal an inverse correlation between serum IgE concentration, which reflects IL-4 and IL-13 activity, and severity of reinfection with this parasite.^{108,109} Studies of patients infected with *Strongyloides stercoralis* reveal an inverse correlation between serum IgE levels and the number of parasite larvae in stool.¹¹⁰ Similarly, high levels of eosinophilic cationic protein and IgE antibody to an *Ascaris lumbricoides* antigen are associated with decreased susceptibility to infection with this parasite.¹¹¹ Furthermore, infection with human T lymphocyte virus-1, which causes an increase in IFN- γ production and decreases in IL-4 and IgE levels, is associated with exacerbation of *Strongyloides stercoralis* infection.^{112,113}

Although data are skimpy, they also are consistent with the possibility that decreased production of T_H2 cytokines may be involved in the pathogenesis of several inflammatory disorders. IL-4 and IL-13 suppress production of inflammatory mediators and reactive molecules by human neutrophils and macrophages. Human type 1 diabetes mellitus, multiple sclerosis, and Crohn's disease resemble rodent nonobese diabetic, experimental allergic encephalitis, and inflammatory bowel disease models in that they are associated with a predominantly T_H1 cytokine responses.^{101,102,114} It has not been demonstrated that enhancement of a T_H2 cytokine response will ameliorate or prevent these disorders; however, a mild, self-limited intestinal

worm infection with the pig parasite *Trichuris suis* has induced remarkable remissions in some patients with Crohn's disease,¹¹⁵ and clinical trials that will determine whether increased IL-4 production will decrease the likelihood of developing type 1 diabetes mellitus are in progress.

IMPLICATIONS FOR THE THERAPY OF ALLERGY AND ASTHMA

Clinical trials have already begun to assess whether neutralization of T_H2 cytokines, blockade of their receptors, or neutralization of IgE are therapeutic for patients with allergic disorders, including asthma, and initial results appear promising. The studies discussed here raise the specter that such therapies will increase the risk of nematode infections, as well as the likelihood of development of T_H1 cytokine-related inflammatory disorders, such as type 1 diabetes mellitus, multiple sclerosis, Crohn's disease, rheumatoid arthritis, and sarcoidosis. It is impossible to accurately gauge such risks without clinical trials; however, we believe that some commonsense precautions will minimize such risks:

1. Such therapies should be avoided in individuals who live in regions of the world in which nematode infections are common, and behaviors that increase the risk of nematode infection (travel in endemic areas that have poor sanitation, ingestion of raw or partially cooked fish and livestock, ingestion of meat from incompletely cooked game) should be avoided in patients who are being treated with these agents.
2. Until the risk of acquiring T_H1 cytokine-related disorders in patients treated with IL-4/IL-13/IL-4 receptor antagonists has been established, we suggest that these therapies should be avoided in patients who have T_H1 cytokine-related inflammatory diseases or a strong family history of these diseases.
3. Treatment with these agents should not attempt to totally eliminate the T_H2 cytokine response but rather should try to shift the T_H1/T_H2 cytokine balance back toward a more normal range.
4. Patients receiving these treatments, at least in initial trials, should be monitored for the development of nematode and ectoparasite infections and the T_H1 cytokine-associated inflammatory disorders.
5. Consideration should be given, where feasible, to the use of local, rather than systemic, drug delivery in disorders such as asthma and allergic rhinitis.

These precautions may turn out to be unnecessary and could be abandoned or scaled back if clinical trials demonstrate that concern about worm infection or T_H1 cytokine-related inflammatory disease is unwarranted. If clinical trials produce evidence that such risks are real, the risks should be balanced against the possible benefits of treatment and the very real and often severe side effects of conventional therapies.

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