REVIEW: IMMUNOLOGY

Allergy, Parasites, and the Hygiene Hypothesis

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The increase of allergic diseases in the industrialized world has often been explained by a decline in infections during childhood. The immunological explanation has been put into the context of the functional T cell subsets known as T helper 1 (T_H1) and T helper 2 (T_H2) that display polarized cytokine profiles. It has been argued that bacterial and viral infections during early life direct the maturing immune system toward T_H1, which counterbalance proallergic responses of T_H2 cells. Thus, a reduction in the overall microbial burden will result in weak T_H1 imprinting and unrestrained T_H2 responses that allow an increase in allergy. This notion is contradicted by observations that the prevalence of T_H1-autoimmune diseases is also increasing and that T_H2-skewed parasitic worm (helminth) infections are not associated with allergy. More recently, elevations of anti-inflammatory cytokines, such as interleukin-10, that occur during long-term helminth infections have been shown to be inversely correlated with allergy. The induction of a robust anti-inflammatory regulatory network by persistent immune challenge offers a unifying explanation for the observed inverse association of many infections with allergic disorders.

There has been a significant increase in the prevalence of allergic diseases over the past 2 to 3 decades. Currently, more than 130 million people suffer from asthma, and the numbers are increasing (*1*); nevertheless, there is a considerably lower prevalence of allergic diseases in developing countries (*2*). There are also clear differences in the prevalence of allergies between rural and urban areas within one country. For example, in Ethiopia, asthma is more prevalent in urban areas than in rural villages (*3*), and asthma is more common in residents of urban Germany than in farmers living in rural Bavaria (*4*). To explain these observations, environmental factors associated with more industrialized and urban living have been studied intensively, but there is little consistent evidence to suggest that obvious risk factors, such as increased exposure to indoor allergens, pollution, or changes in diet and breastfeeding, could account for the rise in atopic diseases. However, another category of environmental factors, childhood infections, shows an overwhelming and consistent negative association with atopy and allergic diseases. Allergic sensitization is overrepresented among first-born but is less frequent in children from large families (*5*) and those attending day care (*6*), suggesting that a frequent exchange of infections may have a protective effect (*5*).

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Atopy, characterized by raised immunoglobulin (Ig)E levels, underlies allergic diseases such as asthma, rhinoconjunctivitis, and eczema. The interaction of an environmental allergen with the innate immune system, its uptake by antigen-presenting cells, and the subsequent T cell priming leads to the stimulation of cytokines such as interleukin (IL)-4, IL-5, and IL-13. These cytokines interact with their receptors to stimulate IgE production and increased numbers of eosinophils and mast cells; all of these components are capable of precipitating inflammation in the respiratory tract (Fig. 1) (*7*).

Exposure to food and orofecal pathogens, such as hepatitis A, *Toxoplasma gondii*, and *Helicobacter pylori*, reduces the risk of atopy by >60% (*8*). Studies of gut commensals indicate differences in the rate of microbial colonization, as well as the bacterial type involved (clostridia versus lactobacilli) in children with and without a predisposition to allergy (*9*). On the basis of these data, it has been proposed that the lack of intense infections in industrialized countries owing to improved hygiene, vaccination, and use of antibiotics may alter the human immune system such that it responds inappropriately to innocuous substances. This so-called "hygiene hypothesis" (*5*) has been given an immunological framework in which the balance between type 1 (T_H1, associated with bacterial and viral infections and autoimmune diseases) and type 2 (T_H2, associated with helminth infections and allergic diseases) immune responses is pivotal (*10*). It has been postulated that limited exposure to bacterial and viral pathogens during early childhood results in an insufficient stimulation of T_H1 cells, which in turn cannot counterbalance the expansion of T_H2 cells and results in a predisposition to allergy (Fig. 1).

The immunological explanation for the hygiene hypothesis has been very influential in directing strategies to prevent allergic diseases. Induction of allergen-specific T_H1 responses by Bacille Calmette-Guerin (BCG) or DNA vaccination is being advocated (*11*) on the basis of the promising results obtained in experimental animals (*11*). However, in the face of discrepancies that have come to light from studies involving autoimmune diseases and helminth infections, it is important to reevaluate the immunological basis of the hygiene hypothesis.

The prevalence of type 1 diabetes, a T_H1-mediated disease, has been progressively increasing in the past few decades, and there are data to support an association between the occurrence of type 1 diabetes and asthma at the population level (*12*). Such data suggest that the root cause of the increase in allergic diseases is also responsible for the escalation of autoimmune disorders and that this cannot merely be accounted for by the T_H1 versus T_H2 imbalance, but instead must have a common immunological denominator. Similar concerns arise when considering helminth infections, which are the most potent natural stimuli for T_H2 responses.

Worldwide, helminth infections and allergic diseases do not overlap despite both conditions being accompanied by strong T_H2 immune responses (*2*, *13*). Here, we review the relation between parasitic infections and allergy and focus on insights that may present an alternative immunological framework for the hygiene hypothesis and have important implications for future research and therapeutics.

Risk Factors or Protection?

Helminth infections are universally associated with responses stimulated by T_H2-type cytokines, such as high levels of IgE, eosinophilia, and mastocytosis (*14*). Thus, although helminth infections and atopic diseases are associated with similar immunological phenomena, the clinical outcome with respect to immediate hypersensitivity and inflammation is clearly not the same (Fig. 1). When one considers that the 1 billion or so people who are heavily infected with helminths worldwide and suffer from the resultant nutritional, growth, and cognital deficiencies are rarely afflicted by allergic diseases, then it is clear that a strong T_H2 response is not the sole factor in precipitating an allergic attack.

The 1960s and 1970s were marked by lively debates about the notion that helminths have a protective effect against allergy. In addition to anecdotal reports of protection from hay fever by ingestion of *Ascaris* spp. (roundworm) eggs (*15*), a meta-analysis of data from early surveys showed that, despite the variation in methodology and clinical assessment of allergy, the prevalence of parasitic infections was negatively associated with the prevalence of asthma (*13*).

More recent studies have reevaluated findings in South America and Africa using a combination of parameters to assess allergy with careful parasitological diagnosis and have shown a consistent inverse relation between helminth infections (schistosomiasis and intestinal helminths) and either skin reactivity to environmental allergens or clinical scores, such as airway hyperresponsiveness, wheeze, and asthma (*16–20*) (Fig. 2A). In most of these studies, >30% of the studied subjects carried substantial levels of IgE to house dust mite (HDM-IgE); these values correspond to those seen in many industrialized countries. In high-income countries, allergen-specific IgE leads to skin reactivity to mite, but in less developed countries, the presence of specific IgE does not always translate into equivalent numbers of atopic skin reactions. In Gabon, only 11% of the school children reacted to mite in a skin prick test (SPT), whereas 32% were positive for HDM IgE (*19*). High levels of IgE and SPT positivity in affluent societies in central Europe (33%) (*21*) and Australia (32.5%) (*22*) are associated with high prevalences of airway disease (12% asthma in central Europe and 21.9% wheeze in Australia). By contrast, in many low-income countries, such as The Gambia (*20*) and Nigeria (*22*), 35.3% and 28.2% atopic reactions translated into only 3.6% asthma and 6% wheeze, respectively. In a recent study in Ethiopia, atopy to HDM was common, but in the presence of high-intensity intestinal helminth infections was unrelated to wheeze (*23*). It is clear, therefore, that despite IgE sensitization to environmental allergens, helminth-infested subjects are somehow protected from mast cell degranulation and inflammatory responses in affected organs.

The burden and chronicity of helminth infections is an important variable that may determine whether helminths act as a risk factor for, or confer protection against, allergic diseases. In Venezuela, the classification of helminth-infested populations into those with none, light, or heavy worm burdens shows that light helminth infections are associated with the amplification of allergen-specific IgE responses and a high skin reactivity, whereas heavily parasitized subjects are protected from atopic skin reactivity despite a high degree of sensitization to mite (*16*). Clinical allergic symptoms in those with light

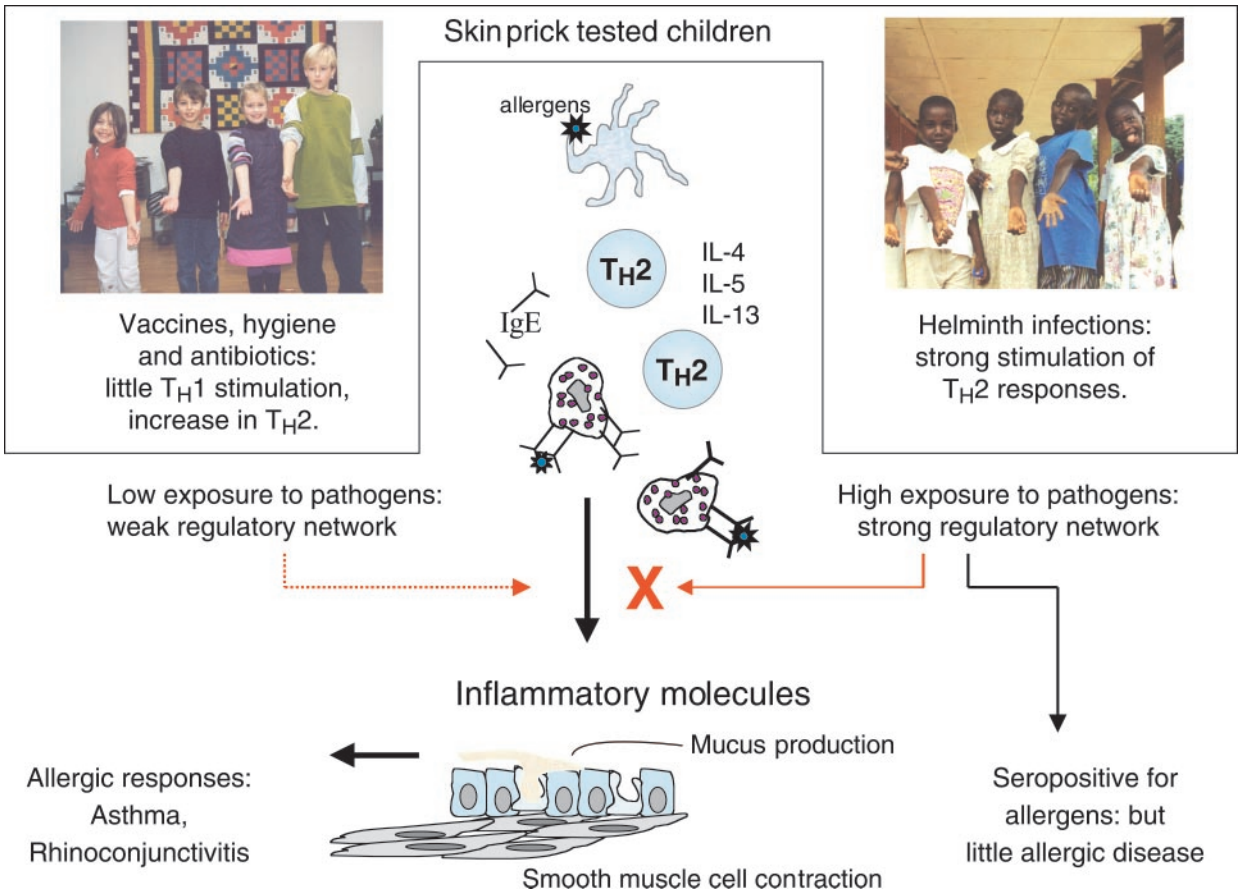

Fig. 1. Divergent outcome of T_H2 responses in industrialized (low pathogen exposure) and developing countries (high pathogen exposure). It has been argued that improved hygiene, frequent use of antibiotics, and vaccination has led to reduced bacterial and viral infections in industrialized countries and therefore to insufficient stimulation of T_H1 responses, which in turn allows the expansion of T_H2 cells. T_H2 responses are characterized by increased IgE to allergens, mastocytosis, and eosinophilia. Mast cell degranulation and release of inflammatory mediators leads to mucus production and smooth muscle cell contraction, precipitating allergic diseases of the airways. Helminths are prevalent in developing countries and lead to strong T_H2 responses. Nevertheless, helminth-infected populations show little signs of allergic disorders. This difference may be explained by the differences in exposure to pathogens. A high prevalence of chronic infections in developing countries results in persistent immune challenge, with cycles of infection and inflammation, which is followed by the triggering of anti-inflammatory molecules to restrict immunopathology. This dynamic interaction educates the immune system to establish a robust regulatory network, possibly the key to controlling allergic diseases. Such a network would be weakly developed in industrialized countries with a low pathogen load, allowing inappropriate immunopathological reactions to develop more readily.

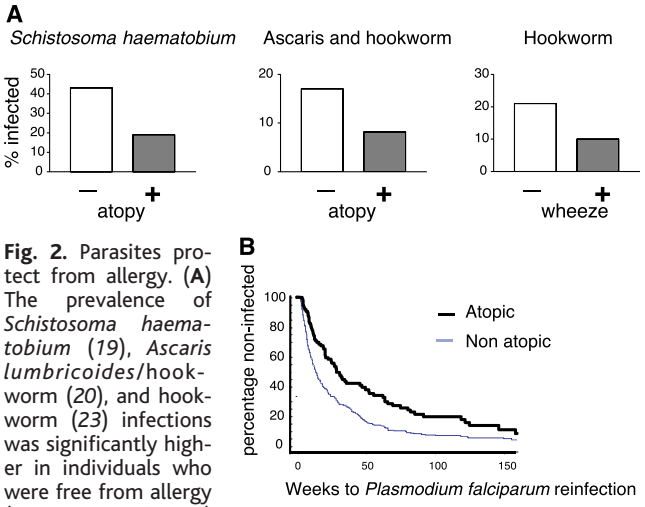

Fig. 2. Parasites protect from allergy. (**A**) The prevalence of *Schistosoma haematobium* (*19*), *Ascaris lumbricoides*/hookworm (*20*), and hookworm (*23*) infections was significantly higher in individuals who were free from allergy (atopy or wheeze) compared to those who were allergic. (**B**) The *Plasmodium falciparum* reinfection scores in young Gabonese children who were either positive or negative in skin testing to HDM (*58*). In the Kaplan-Meier analysis of the data, it was found that nonatopic children (blue line) had significantly shorter periods to reinfection and therefore higher incidences of infection than did atopic children (black line).

helminth infections were alleviated after deworming with drugs (*24*) but were exacerbated in individuals who had had heavy worm burdens (*17*). This reinforces the view that heavy helminth infections protect against allergy. These observations may also explain the situation in industrialized countries where exposure to helminths such as *Toxocara* spp. (*25*), leading to seropositivity, is associated with an increased prevalence of airway symptoms. Such infections are presumably light and sporadic, allowing exposure to helminth antigens that potentiate T_H2 responses without the inhibitory component that is associated with heavy and chronic infections.

Polyclonal IgE and Allergic Responses

The first scenario that was favored to explain the negative association between helminths and allergy was the "IgE blocking hypothesis." Clinical allergy requires efficient cross-linking of high-affinity IgE receptors (FcεRI) on mast cells and basophils (*7*). At least two FcεRI-bound IgE molecules must capture a single allergen (bivalent interaction) to induce mediator release. Helminth infections are often associated with highly polyclonal IgE, which is not specific for parasite antigen. If IgE, for which no antigen is available, saturates FcεRI on mast cells and blocks the binding of specific IgE directed either to parasite antigen or to environmental allergens, it could inhibit degranulation and immediate hypersensitivity responses to allergens. In an editorial in the *Lancet* in 1976, it was proposed that "one theoretical approach to prevention or treatment of allergic diseases would be deliberately to induce high IgE responsiveness—for example, by artificial infection with parasites" (*26*). In numerous immunoepidemiological studies, the protective effect of helminth infections on allergic reactivity was associated with high levels of total polyclonal IgE (*16*, *17*, *27*, *28*). What was considered compelling data for the ability of total IgE to protect against mast cell degranulation came from early studies using the Prausnitz-Kustner (P-K) test, which is based on passive sensitization of mast cells by the dermal injection of a serum containing high allergen-specific IgE, followed by a skin challenge with the allergen to induce a wheal and flare reaction. With one exception (*29*), the studies showed that, in recipients with high levels of IgE, it was not possible to sensitize for skin reactivity to an allergen (*16*, *17*).

Several arguments have been raised against this model. First, the epidemiological association studies did not take into account the effect of confounding factors such as age, sex, nutrition, socioeconomic factors, or the immunological parameters tested. Recent studies in Gabon and Ethiopia, where confounders were included in the statistical analysis, failed to show any significant effect of total IgE on parasite-mediated suppression of atopy (*19*, *23*). Second, with respect to the P-K test studies, there may be a difference in how total IgE influences the mast cell Fcε receptor occupancy by allergen-specific antibodies administered passively, as opposed to when allergen-specific IgE antibodies are actively produced in vivo. This has been elegantly shown in an experimental model, where IgE induced by a helminth infection was capable of blocking passive sensitization but did not inhibit skin hypersensitivity reactions to an allergen by endogenous, actively produced IgE (*30*). Furthermore, clinical trials with antibodies to IgE have provided direct evidence that the FcεRI numbers on mast cells respond to the concentration of circulating IgE by changing receptor concentration and accommodating additional binding (*31*).

Clinically Irrelevant Allergen-Specific IgE Antibodies: Cross-Reactivity

The characteristics of the specific IgE antibodies against common inhalant allergens may contribute to a high prevalence of sensitization to allergens without clinical symptoms in parasite-infected subjects. Clinically irrelevant specific IgE antibodies are not unique to parasite-infected patients. Pollen-allergic patients often have IgE antibodies against foods without any sign of clinical food allergy (*32*). Common structural elements, such as peptides in *Betula verrucosa* allergen 1 and profilins or α(1,3)-linked fucose on proximal N-acetyl-glucosamine in glycoproteins play an important role in IgE cross-reactivity between pollen and food allergens (*33*). Pollen-allergic patients with IgE antibodies against these sugars or against the cross-reactive peptides are positive for in vitro diagnostic tests for many vegetable foods, yet skin reactivity with vegetable foods is low or absent in many of these pollinosis patients (*32*). Whether cross-reactive IgE is of low affinity and therefore unable to induce efficient mediator release from mast cells is not yet known.

In most studies of allergy in the tropics, prominent reactions to the HDM are reported. Although structural data on the N-glycans of these invertebrates has not been reported, α(1,3)-linked fucose is present on glycoproteins of other arthropods (*34*). This substitution has recently been identified as an IgE-binding structure in helminths (*35*). Similarly, parasitic antigens, such as tropomyosins and glutathione *S*-transferases, have their allergenic homologs in HDMs (*36*). It is therefore tempting to speculate that chronic helminth infections result in IgE responses that are cross-reactive to HDM; hence, by analogy with cross-sensitization from pollen to foods, sensitization to parasites may induce clinically irrelevant cross-reactions to HDMs. Preliminary studies of one cohort in Gabon do not support an important role for cross-reactivity between helminth and mite antigens (*37*), but more research is needed on the biochemical characterization of IgE to HDM in tropical populations. With the availability of reagents, both recombinant allergens, and synthetic glycans, it is now possible to study the bimolecular interactions of IgE with well-defined epitopes.

Although the IgE-blocking hypothesis appears to be obsolete, and the proposition that the physiochemical characteristics of the IgE-recognizing allergens in parasitized populations contributes to the low incidence of clinical allergy has yet to be tested, data from recent studies on hyporesponsiveness and anti-inflammatory cytokines have indicated attractive explanations for the low levels of allergy in T_H2-skewed populations.

Alternative T_H2 Responses: The IgG4 Isotype

For helminth parasites, it is known that asymptomatic infections are correlated with high levels of IgG4, another T_H2-dependent isotype, and it has been shown that parasite-specific IgG4 antibodies can inhibit IgE-mediated degranulation of effector cells (*38*). Originally, this concept of

"blocking" antibodies was proposed as a possible mechanism of allergen immunotherapy in the 1930s and 1940s (*39*). Efficient treatment of allergic patients by immunotherapy consists of immunization with increasing doses of allergen up to a maintenance dose, which is then administered at regular intervals (fortnightly or monthly) for at least 3 years. It has been noted that one of the characteristics of successful immunotherapy is the induction of allergen-specific IgG4 antibodies, even with the persistence of allergen-specific IgE (*40*). A recent report from Platts-Mills showed that a high exposure to cat allergens results in high IgG4 titres and decreased atopy, supporting a role for IgG4 antibodies in down-regulating allergic responses (*41*). Platts-Mills *et al*. propose the term "alternative T_H2 responses" to describe a modified T_H2 response not associated with clinical allergy, a concept that has also been invoked in autoimmunity (*42*). It is therefore tempting to propose that the lack of skin reactivity in parasitized individuals may be due to the presence of blocking IgG4 antibodies. Although not investigated extensively, a study in Gabon found no evidence for an inverse correlation between IgG4 and skin reactivity (*37*). The question of whether IgG4 competes for allergen or whether its occurrence reflects another immunologic event that underlies the lack of allergy should be considered given that the immunosuppressory cytokine IL-10 has recently been shown to stimulate IgG4 differentially (*43*). High levels of IL-10 are seen in individuals chronically infected with helminths (*44*) and subjects receiving allergen immunotherapy (*45*), conditions that are associated with high IgG4.

The Anti-Inflammatory Network May Be Central to the Hygiene Hypothesis

T cell hyporesponsiveness is a well-known corollary of chronic parasitic infections in humans. Helminth parasites in particular are associated with poor antigen-specific T cell–proliferative responses, as well as with reduced cytokine production (*44*). Down-regulatory molecules such as IL-10 (*44–46, 47*), transforming growth factor beta (TGF-β) (*47*), and nitric oxide (*48*) have been implicated in this immunosuppression, and clear evidence for elevated IL-10 has come from studies on filarial and schistosomiasis patients. The helminth antigen–specific immunological hyporesponsiveness appears to spill over to nonrelated antigens. Work on immunological responses to a purified protein derivative of *Mycobacterium tuberculosis* (PPD) and to tetanus toxoid after BCG or tetanus vaccination has shown that responses are weaker in patients with concurrent helminth infections, as compared with responses in healthy controls (*49*, *50*). The immunosuppressive effects of chronic helminth infections can be transferred to a fetus in utero; children born to mothers infected with filarial worms or with schistosomes respond poorly to BCG (*51*). Therefore, it is clear that the wiring of immune responses in populations living in tropical countries and exposed to a multiplicity of chronic helminth infections can be quite distinct from those in subjects living in regions where infections have been controlled more successfully.

This may have several important implications for the expression of immune-mediated diseases, such as allergy. As already noted, allergies are inflammatory diseases dependent on T_H2-type responses and initiated by mast cell degranulation. The release of mediators leads to vasodilation, mucus production, and smooth muscle cell contraction and accompanies the production of pro-inflammatory cytokines (Fig. 1). Therefore, the presence of a strong anti-inflammatory regulatory network, characterized by elevated IL-10 and TGF-β produced by antigen-presenting cells, and/or the newly discovered regulatory T cells (*52*), could help to prevent the cascade of events leading to allergic inflammation (Fig. 1). Recent data on schistosomiasis and atopy in Gabon support this view (*19*). When all immunological parameters are taken into consideration, parasite-induced IL-10 significantly reduces (by 47%) the risk of skin reactivity to mite.

Several studies in industrialized countries of patients with allergic diseases favor a central role for anti-inflammatory cytokines. Allergic individuals express lower levels of IL-10 (*53*), and the skin-wheal size in response to mite is negatively correlated with allergen-stimulated IL-10 (*54*). Moreover, successful immunotherapy is associated with a sharp increase in IL-10 production by T cells (*45*) and IL-10 increases in atopic children receiving probiotic supplementation (*55*). Royer and colleagues (*56*) have shown that IL-10 can inhibit mast cell degranulation, providing a mechanism for the observed negative associations between IL-10 and atopy.

Nature of the Pathogen and Induction of the Regulatory Network

Although helminth infections have highlighted the inability of the T_H1-T_H2 dichotomy to explain the hygiene hypothesis and have provided an alternative explanation based on the anti-inflammatory network, it has to be emphasized that several other chronic infectious diseases are associated with down-regulated inflammatory responses. For example, malarial parasites infect a large proportion of children worldwide and is associated with profound immunosuppression (*57*). Recently, malaria has been linked to allergy; in a study conducted in a cohort of young children in Gabon, malaria infections were intensively monitored (every 2

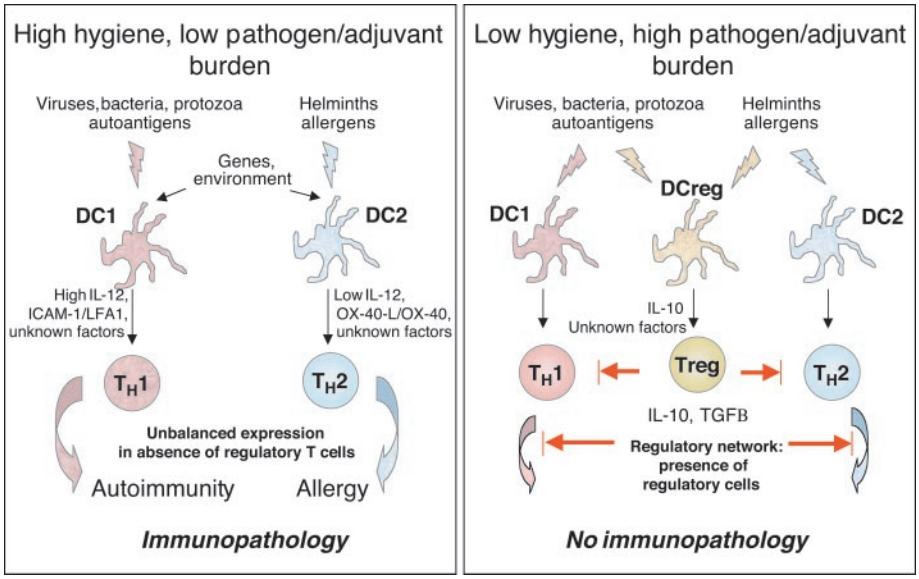

Fig. 3. Education of the immune system by pathogens. Dendritic cells can develop into distinct subpopulations, depending on the nature of the signals they receive from the microenvironment, and then direct T cell differentiation into polarized subsets. Viruses, bacteria, and helminths carry distinct signature molecules that interact with dendritic cells to stimulate T_H1-type and T_H2-type immune responses (*63*). When uncontrolled, strong T_H1 and T_H2 responses lead to autoimmunity and allergy. High pathogen burden may either change the physiology of the microenvironment or result in the accumulation of novel signature molecules that together endow dendritic cells with the ability to induce regulatory T cells. Regulatory T cells produce suppressory cytokines and are part of an anti-inflammatory network that ensures that inflammatory T cells (both T_H1 and T_H2) and their downstream effectors are kept under control.

weeks) for 5 years, at the end of which the patients were skin tested for mite. As shown in Fig. 2B, children who had a negative SPT had significantly shorter periods between infections, and thus higher scores of repeated infections in the observation period (*58*). These results agree with studies showing that responses to other severe infectious diseases in the tropics such as measles and tuberculosis are inversely associated with atopy (*59*, *60*). Notably, each of these diseases is associated with immunosuppression sometimes mediated by IL-10 or TGF-β (*61*, *62*).

Immune activation or suppression has been closely linked to dendritic cells, which acquire signals from the microenvironment and convey these to naïve T cells, instructing their development into polarized T_H1, T_H2, or regulatory T cells (*63*, *64*). Thus, although helminths induce the development of type 2 responses, and viruses and bacteria skew toward type 1 (*63*), it is possible that high overall infection turnover is instrumental to the development of the regulatory network, as depicted in Fig. 3. The model also raises the question whether certain pathogens carry signature molecules that are better suited to induce regulatory cells and to protect against atopy than other pathogens and predicts that frequent antigenic challenge from an array of pathogens is needed for a balanced development of the immune system and the prevention of allergic and inflammatory diseases (*10*, *42*). However, instead of T_H1 versus T_H2, it may be the pro- versus anti-inflammatory axis with a robust regulatory T cell network that has to be considered central to the balance and to the prevention of either T_H1 and/or T_H2 diseases (Fig. 3) (*14*, *42*).

Implications for Therapeutics and Future Research

The parallels between parasite infections and immunotherapy strongly suggest that strategies for successful prophylaxis should be focused on the induction of an anti-inflammatory response rather than on active induction of an allergen-specific T_H1 response. The latter strategy may be particularly dangerous when data are considered from experimental models of asthma that show that the transfer of T_H1 cells exacerbates rather than suppresses airway inflammation (*65*). IL-10 therapy to control autoimmune and allergic diseases has been suggested before (*66*). The most effective strategy has yet to be determined, because administration of IL-10 to Chron's patients did not improve clinical scores (*67*), suggesting that stimulation of the immune system for an early and intrinsic production of IL-10 or other regulators may be essential. It is now well established that recently discovered regulatory T cells, important players in the anti-inflammatory network, can suppress the development of harmful pathology to specific antigens (*52*). Efforts should now focus on more efficient manipulation of regulatory T cells to imprint allergen specificity for therapeutic purposes without hampering the efficacy of the routine childhood vaccination. The observation that the repeated stimulation of the immune system by pathogens is central to the development of a balanced regulatory system also highlights the need to identify molecular patterns on parasites and to study their immunomodulatory potential. The issues discussed in this review may also have implications for genetic studies. The consideration that pro- versus anti-inflammatory immune responses may hold the key to the development of allergic diseases implies that the focus of genetic studies may have to be upstream of T_H1 and T_H2, concentrating on genes involved in the control of inflammation. With respect to epidemiological studies, studies on human populations in the tropics who carry varying burdens of diverse pathogens would complement studies on the hygiene hypothesis in industrialized countries by providing crucial information on the optimal dose of infection challenging the immune system, the importance of a mother's infection status on her infant, and the pathogens having superior immunomodulatory capacity.

Parasites are often long-lived and inhabit immunocompetent hosts for prolonged periods; consequently, it is not surprising that they should possess modulatory molecules that ameliorate host responses to enhance their survival. Understanding the genetics of host-parasite interaction and identifying the distinct parasite molecules that have immunomodulatory effects will help us combat allergy without paying the price of becoming infected with noxious pathogens.

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