

Atopic disorders: a default pathway in the absence of infection?

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Allergic responses to common environmental antigens, such as those derived from house dust mites, plant pollens or animal proteins, lead to clinical disorders such as asthma, hay fever, eczema and allergic rhinitis. The reasons why only some individuals develop these atopic disorders are poorly understood. The current view is that genetic and environmental factors interact with each other, leading to the production of interleukin 4 (IL-4) through Stat6-mediated signalling and the activation of specific downstream transcription factors such as c-Maf, GATA3, NIP45 and NFATc in naive T cells, resulting in the development of allergen-specific T helper 2 (Th2) CD4⁺ T cells. Once generated, Th2 cells activated by allergen secrete IL-4 and IL-5, cytokines that induce the production of IgE and IgG1 by B cells, as well as stimulating the development of eosinophils in the bone marrow and their recruitment into inflamed tissues^{1–6}.

It is believed that the most important factor governing the pathogenesis of atopic disorders is the crosslinking of IgE Fcε receptors on mast cells, after encountering allergen, which leads to mast cell degranulation. The molecules released by mast cells include histamine, heparin and proteases, which mediate biological effects including vasodilatation, intestinal and/or bronchial smooth muscle contraction, mucous secretion and local proteolysis. After the initial immediate reaction of the mast cells, an influx of eosinophils, basophils and lymphocytes occurs, 6–24 h later. This late-phase response can lead to chronic inflammation of tissues continuously exposed to antigen. This course of events is especially evident in asthmatic disease, where chronic swelling and inflammation of the airways can lead to a sudden and violent constriction upon allergen challenge^{1,2}. What follows will be a discussion of how some infectious diseases may influence both the development of allergic disorders and their effector mechanisms.

Influence of infectious diseases on atopy

The incidence of atopic disorders, in particular asthma, is increasing in developed as opposed to developing countries, with ~20–30% of the population affected^{7,8}. The reason for this discrepancy is not clear and there are several possible reasons that could account for it. First, the genetic background of the human population living in developed versus third world countries could be different, resulting in a

Atopic disorders, such as asthma, are increasingly prevalent in the developed world. Recent epidemiological and experimental data suggest that some infectious diseases prevalent in the developing nations can inhibit the development of allergic disorders. Here, Klaus Erb reviews the data and presents a model showing how a steady decline of infectious diseases could account for an increase in atopic disorders.

higher propensity to atopic disease. However, this appears not to be the case, as people from developing countries show an increase in allergic diseases when they are exposed to Western living conditions⁹. Interestingly, it has also been suggested that the increase in atopic disorders observed in former East Germany might be partly due to an increase in westernization¹⁰. A second hypothesis is that, within developing nations, a lower level of industrial pollution results in lower atopy rates. However, the atopy rate of people living in highly polluted regions of Poland or the former East Germany is lower compared with those living in substantially less polluted Sweden or West Germany^{11,12}.

Finally, it has been speculated that the increase in atopy is due, in part, to the steady decline of infectious diseases in the developed world. Recent epidemiological studies demonstrating an inverse relationship between atopy and immunization/infection with mycobacteria, measles or hepatitis A (Refs 13–15) appear to provide support for this hypothesis.

Infectious diseases and Th1-type immune responses

How can infectious diseases suppress the development of atopic disorders? Diseases such as measles, whooping cough, influenza and tuberculosis induce Th1-type responses, which lead to an immunological environment rich in interferon γ (IFN-γ)^{16–18}. IFN-γ plays a role in the suppression of Th2 immune responses both *in vivo* and *in vitro*^{19–25}. Szabo *et al.*²⁶ presented a model suggesting that naive T cells, after activation by antigen-presenting cells (APCs) and in the absence of IL-4, express both the α- and β-chain of the IL-12 receptor, thus facilitating IL-12-mediated Th1-cell development. In the presence of IL-4, however, expression of the IL-12 receptor β-chain is repressed, resulting in Th2-cell development. The β-chain of the IL-12 receptor is expressed in the presence of IFN-γ, irrespective of the presence of IL-4, thus stimulating Th1-cell development among the pool of naive T cells.

An intriguing possibility is that the Th1 environment promoted by infectious diseases might hamper the development of allergen-specific Th2 cells and prevent the consequences of this development (atopic disorders). A number of studies support this view. In particular, Kline *et al.* demonstrated that treatment of mice with CpG-motif oligonucleotides inhibited the development of allergic airway inflammation²⁷. These CpG-motifs are derived from bacterial DNA

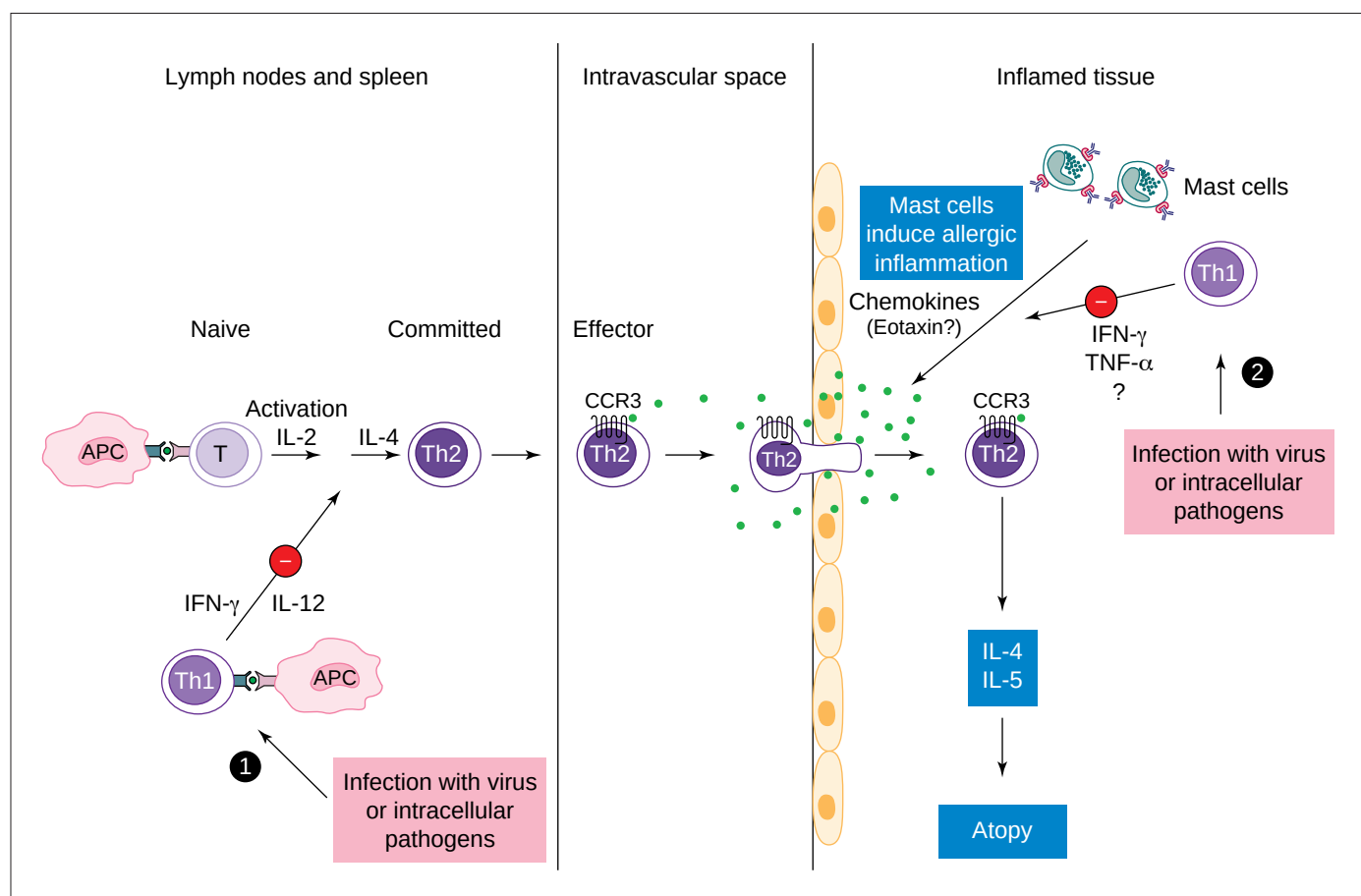


Fig. 1. Proposed inhibition of atopic disorders by infections that induce Th1 immune responses. APCs take up allergens and present peptides to naive T cells in the spleen and lymph nodes. Genetic and environmental factors then determine whether IL-4 is present during the priming and proliferation of the naive T cells, which would lead to the generation of allergen-specific Th2 cells. Effector Th2-type cells express the CC chemokine receptor 3 (CCR3) and circulate in the bloodstream. Allergic inflammation in the tissue increases the production of eotaxin. Eotaxin binds to the CCR3 on the circulating Th2 cell, enabling the cells to home into the inflamed tissues. Upon stimulation with allergen, large amounts of IL-4 and IL-5 are secreted by the Th2 cells. The production of IL-4 induces the production of allergen-specific IgE, which binds with high affinity to mast cells. IL-5 production leads to the development of eosinophils in the bone marrow and is involved in the recruitment into the airways. Infections inducing Th1 immune responses may inhibit the development of allergen-specific Th2-type cells in the spleen and lymph node by providing IFN- γ and IL-12 at the site of naive T-cell priming (1). Furthermore, Th1 responses at the site of allergic inflammation may inhibit the production of chemokines necessary for the efficient homing of Th2 cells into these sites, further suppressing the development of atopy (2). Abbreviations: APC, antigen-presenting cell; IFN- γ , interferon γ ; IL-2, interleukin 2; Th1, T helper 1; TNF- α , tumour necrosis factor α .

(they are rarely seen in eukaryotic DNA) and have been shown to induce the production of IFN- γ by natural killer (NK) cells²⁸. This finding suggests that exposure to bacterial DNA during infection also inhibits the development of atopic disorders. Furthermore, it has been demonstrated that *M. bovis*-BCG infection can suppress the development of allergen-induced airway eosinophilia²⁹ and airway hyper-responsiveness in mice³⁰. One possible explanation for these results is that the IFN- γ produced during the Th1 response directly inhibits the development of allergen-specific Th2 cells through the mechanism described above by Szabo *et al.*²⁶ However, there may also be other mechanisms by which infections inhibit the development of an allergic phenotype. For example, the cytokine environment induced by Th1 responses may direct naive Th cells towards Th1- and away from Th2-cell development by suppressing the expression of transcription factors needed for the differentiation of Th2 cells and/or inducing the production of transcription factors

responsible for the generation of Th1 cells. Furthermore, Th1 immune responses could somehow inhibit the expression of chemokines normally induced during allergic inflammation, which are essential for efficient homing of eosinophils and Th2 cells into the inflamed tissues (Fig. 1). A possible candidate is eotaxin (predominantly produced by lung epithelial cells and alveolar macrophages), which is expressed during allergic inflammatory responses^{31,32}. In addition, Th2 but not Th1 cells express a receptor for eotaxin, the CC chemokine receptor 3 (CCR3)^{33–35}. Therefore, it may be possible that strong Th1 responses in the lung downregulate or alter the kinetics of eotaxin expression and possibly other chemokines during allergic inflammation, thus suppressing the development of an atopic phenotype. However, this mechanism may not involve the typical Th1 response-associated cytokines, tumour necrosis factor α (TNF- α), IL-1 β and IFN- γ , because these cytokines increase the expression of eotaxin mRNA in epithelial cell lines³⁶.

Although it seems clear that infections that induce Th1 responses have the capacity to inhibit Th2 responses, there may be situations where this does not occur. For example, infections with *M. bovis*-BCG strongly inhibited the development of a local Th2 response in the lung but not the systemic allergic response^{29,30}. This suggests that the infection needs to occur at the same site as the allergic response to have the maximal suppressive effect. If this is not the case, it is plausible that Th1 and Th2 responses can coexist simultaneously at different sites in the body. Furthermore, the time point of the infection in respect to the age of the individual may also be crucial for the suppression of the atopic phenotype. The neonatal immune response of non-atopics is biased towards Th2 responses, which then shift towards Th1 responses during the first years of life. By contrast, children who become atopic do not lose the Th2 response. A recent report attributed the lack of Th2 response suppression in atopic children to the inability of these children to produce sufficient amounts of IFN- γ as neonates³⁷. This suggests that infectious diseases that induce the production of IFN- γ should have the greatest impact on the inhibition of atopic disorders during the immediate postnatal period or early childhood, with infections later in life having no suppressive effect. The observation that non-atopic

children develop allergen-specific Th1 patterns and not atopy-inducing Th2 patterns before the age of five years³⁸ supports this view.

Influence of post-atopic infectious diseases on the development of allergic disorders

As discussed above, it seems clear that infections that induce Th1-type responses can, under certain conditions, inhibit the development of an atopic phenotype. However, what happens when the infection occurs at the same site after the allergic disorder has already developed fully and has become chronic? It appears that one of two outcomes prevails, depending upon the strength of the Th2 response and thus the amount of IL-4 being produced. The presence of IL-4 during T-cell priming may deviate the normally dominant Th1 response induced by the infectious agent into a mixed Th1/Th2 response, resulting in exacerbation of the atopic disorder. Supporting this view are reports demonstrating that IL-4 can induce the generation of Th2 responses under conditions that normally favour the generation of Th1 cells only³⁹⁻⁴¹. By contrast, if there is a weak allergic response with low levels of IL-4, the Th1 response against the

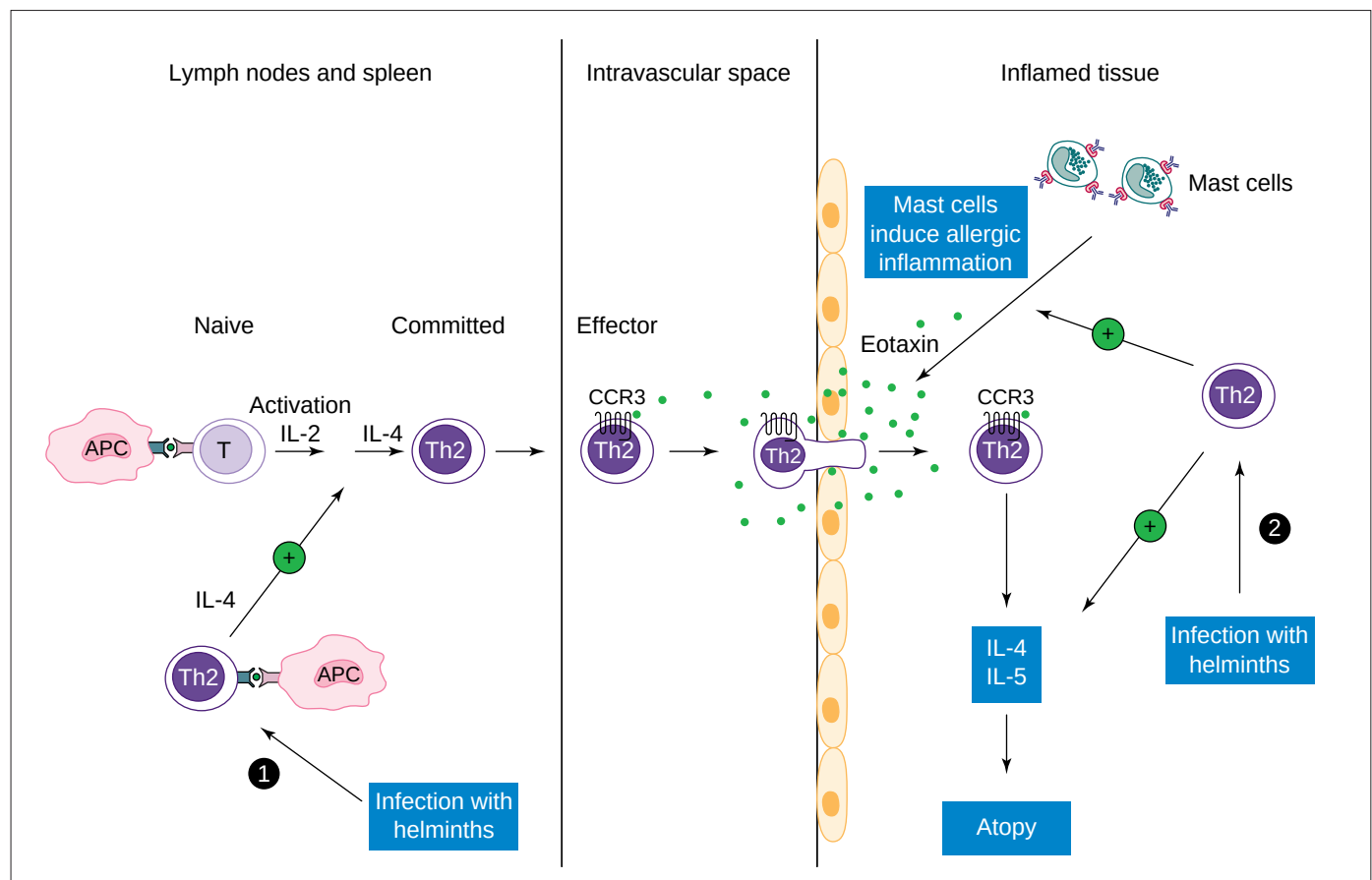


Fig. 2. Possible exacerbation of atopic disorders by infections that induce Th2 immune responses. Infections inducing Th2 responses can increase the development of atopic disorders by directly providing more IL-4 for allergen-specific Th2-cell development (1). Furthermore, if allergic inflammation and the infection takes place in the same tissue, the infection-specific Th2 cells may increase the severity of the atopic disorder by secreting IL-4 and IL-5, and induce the production of chemokines such as eotaxin (2). Abbreviations: APC, antigen-presenting cell; IL-2, interleukin 2; Th1, T helper 1.

infection will probably not be deviated to a mixed Th1/Th2 response. Taken together, it is possible that a Th1 response induced by an infection deviates to a more Th2 type under the influence of a strong allergic response. Although this still remains to be proved experimentally, the clinical observation of infection-induced asthma suggests that this effect can occur.

Another mechanism by which infectious diseases might increase the symptoms of established allergic responses is by providing IL-2 to proliferating, allergen-specific Th2 cells, resulting in stronger Th2 responses. The observations that Th1 cells produce IL-2 and Th2 cells require IL-2 for optimal development⁴² support this idea.

Infectious diseases inducing Th2-type responses

Other infectious diseases that might influence the development of atopic disorders are those involving metazoic worms. In contrast to infections with intracellular pathogens, helminthic worm infections induce very pronounced Th2-type responses^{16–18}. Therefore, worm infections would be expected to promote atopy through the induction of IL-4 expression (Fig. 2) and possibly Th2-cell specific transcription factors in naive T cells, leading to increased development of allergen-specific Th2 cells. Furthermore, the increase in total eosinophil numbers and induction of mastocytosis observed after worm infections⁴³ might directly increase allergic-type inflammation. Mechanical irritation at sites of allergic inflammation during worm migration (for example, ascarids in the lung) may also increase the atopic phenotype by increasing inflammatory responses at these sites in general. This view is consistent with studies showing that IL-4 enhances Th2-cell development^{16–18}, that infections with *Nippostrongylus brasiliensis* induces airway hyperresponsiveness⁴⁴ and that allergic manifestations occur more often in children seropositive for *Toxocara* than in seronegative children⁴⁵. Furthermore, anthelmintic treatment of individuals living in regions with a high prevalence of worm infections also resulted in the improvement of asthma⁴⁶. Interestingly, this phenomenon was only observed when the individuals had a relatively low parasite load, with helminth eradication in children with higher worm loads triggering the induction of atopic disease⁴⁷. Furthermore, in developing countries with a high incidence of helminth infections, atopic disorders are not nearly as common as in developed countries^{7,48}. The basis for

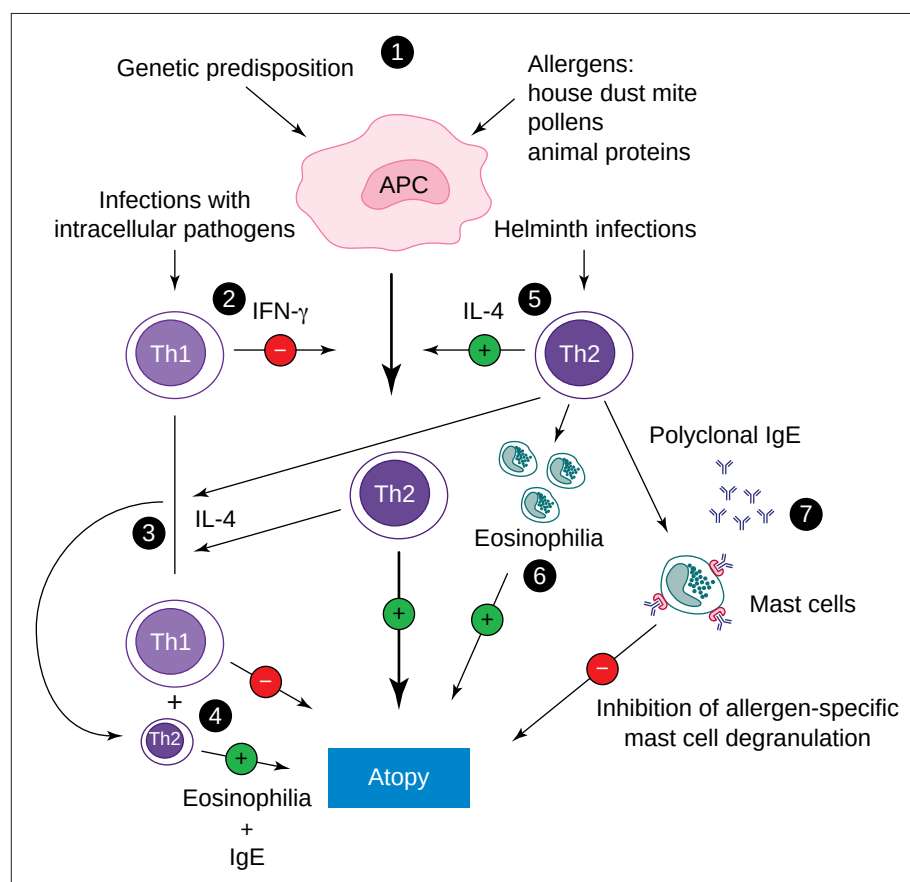


Fig. 3. Model of the possible interactions between infectious diseases and the development of atopic disorders. (1) Genetic and environmental factors determine whether or not allergen-specific Th2 cells are generated; Th2 cells lead to the development of atopic disorders. (2) Infections inducing Th1 responses inhibit the development of allergen-specific Th2 cells by inducing the production of IFN- γ at the site of naive T-cell priming. (3) Established allergic responses or helminth infections deviate Th1 immune responses against pathogens to a mixed Th1/Th2 type by the production of IL-4. (4) Th2 cells specific for the intracellular parasites induce eosinophilia or IgE responses during infection, further exacerbating the development of atopy. (5) Helminth infections directly enhance Th2 responses against allergens by providing IL-4 during allergen-specific Th2-cell development. (6) Increased production and recruitment of eosinophils during worm infections may also contribute to the exacerbation of atopic disorders. (7) The production of polyclonal IgE (induced by metazoic worm infections) competes with allergen specific-IgE binding to mast cells, resulting in the inhibition of mast cell degranulation after allergen challenge. Abbreviations: IFN- γ , interferon γ ; IL-4, interleukin 4; Th1, T helper 1.

these observations is not clear. One possibility is that humans in developing countries may be exposed more frequently to Th1-inducing infections, resulting in the inhibition of atopic disorders, irrespective of worm infections. A further intriguing hypothesis is that although helminth infections might actually increase Th2 responses towards allergens, they may also inhibit atopic effector functions^{7,48}. Helminth infections induce the production of polyclonal IgE, which may saturate the Fc ϵ receptors on mast cells and thus competitively inhibit binding of allergen-specific IgE. In this way, the helminth infection would suppress allergen-mediated mast cell degranulation and the development of atopic disorders. Supporting this hypothesis are reports demonstrating that rats infected with helminths show a suppression of allergic reactivity, as well as that allergic sensitization of human lung fragments could be inhibited by

saturating IgE binding sites^{49,50}. However, the second finding is somewhat controversial, with other groups failing to confirm this data⁵¹.

Although the effects of a helminth infection on allergic responses are not clear, some infectious agents that induce Th2 responses appear to increase the development of atopic disorders. For example, it has been reported that infections with respiratory syncytial virus (RSV) exacerbate asthmatic disease both in humans and mice^{52–54}. Although the immune effector mechanism through which RSV infections mediate this effect is not clear, it is thought to be at least partly due to the direct induction of Th2 responses in the lung by the virus.

Concluding remarks

Taken together, there is good evidence that infections can strongly influence both the development and severity of atopic disorders. Furthermore, in my opinion, it is plausible that the increase in prevalence and severity of atopic disorders observed in developed countries is in part caused by a decrease in infectious diseases afflicting children early in childhood. Infections such as measles, whooping cough, influenza and tuberculosis induce potent Th1 responses and appear to inhibit the development of atopy by either directly suppressing allergen-specific Th2-cell development or by other not yet defined mechanisms. However, this effect might be a double-edged sword because these infections may actually increase the severity of allergic disorders if the infections occur after an atopic phenotype has developed fully. Helminth infections further illustrate the complexity of the interactions mediating the development of allergic disorders. Although the helminth-induced production of IL-4 may increase Th2 responses against allergens, allergic effector mechanisms (IgE-mediated mast cell triggering) might actually be inhibited. However, the long-term prognosis may be a strong exacerbation of atopic disease at the time point when polyclonal IgE levels drop off after natural or medication-induced elimination of the helminths. Figure 3 summarizes a model of how infectious diseases might modulate the development and effector functions of atopic disorders.

The evidence and speculations outlined above have led to a scientific debate focusing on the possible application of attenuated infectious agents as vaccines to aid in the treatment of allergic disorders. Furthermore, it has been suggested that by not vaccinating against childhood diseases, fewer people may develop atopic disorders during their lifetime, although the risks of this approach may outweigh the benefits. In my opinion, such proposals may eventually do more harm than good until we can more completely understand the immune effector mechanisms mediating responses to allergens and infectious diseases.

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