

TAB 13 Background Information on the Hygiene Hypothesis

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Maziak, W. The asthma epidemic and our artificial habitats. *BMC Pulmonary Med.* 2005; 5(1):5.

Note: Material is provided for background information only; it is not required reading.

Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection

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Epidemiological and experimental data suggest that infections or the exposure to non-pathogenic bacteria protect individuals from developing some autoimmune and atopic disorders. Generally, these findings support the 'hygiene hypothesis', which attributes the rise in autoimmune and atopic disorders to a lack of infections that normally keep the immune system balanced by inducing immunoregulation. The suspected key players for infection-mediated immune suppression of autoimmunity and atopy are T regulatory cells and dendritic cells, which produce immunosuppressive cytokines, such as interleukin-10 and transforming growth factor- β . However, there is also solid evidence suggesting that infections can exacerbate or even directly cause autoimmune and allergic disorders. In this Review, we discuss which type of infections induce, exacerbate or inhibit allergic and autoimmune diseases and point at infection-induced immunological mechanisms influencing the development of autoimmunity and atopy.

Introduction

The immune system protects from infectious diseases. Some immune responses attack the organism itself, causing autoimmune diseases, such as type 1 diabetes (T1D) or multiple sclerosis (MS). Immune responses against harmless antigens cause allergic diseases, including rhinitis, atopic dermatitis and allergic asthma. The incidence of autoimmune and allergic diseases has been increasing dramatically in western countries over the past 50 years [1]. It is therefore important to understand how these diseases are triggered, persist and are modulated. Autoimmune diseases are frequently considered to be the consequence of aberrant immune responses against pathogens [1,2]. The development of asthma and allergy, by contrast, might be favored by the absence of infections [3,4]. Here, we review the multiple connections – protective or pathogenic – among infection, autoimmunity and atopy, focusing on viruses, bacteria and helminths.

Protection from, and induction of, autoimmunity by pathogen exposure: mechanisms and examples

Autoimmune diseases occur when T or B cells recognize self-antigens. In autoimmune diseases, Th cells produce inflammatory cytokines and recruit and activate effector cells, ultimately resulting in organ damage. Autoreactive T and B cells are part of the normal immune cell repertoire in healthy humans. Therefore, to understand what triggers these normally quiescent autoreactive lymphocytes is crucial to understanding autoimmune diseases.

The incidence of both autoimmune and atopic diseases is a mirror image of the incidence of some infectious diseases, most notably perhaps mycobacterial and helminthic infections and hepatitis A [1]. Several studies have suggested that infections within the first year(s) of life decrease the risk of developing T1D, inflammatory bowel disease (IBD) or MS [1,5,6]. Exposure to a wide variety of infectious agents, including viruses [1], mycobacteria [7], *Salmonellae* [8] and helminths [9], protects the diabetes-susceptible non-obese diabetic (NOD) mice from spontaneously developing T1D. Although it is not clear which cell type mediates infection-induced protection against T1D in NOD mice, there are some reports indicating that CD4⁺ T cells and natural killer (NK)T cells might have a role. The adoptive transfer of spleen cells from bacille Calmette–Guerin (BCG)-infected NOD mice protect recipients from diabetes; however, the protective effect is lost when CD4⁺ cells are depleted from the transferred cell population [7]. T cells from schistosome-infected NOD mice produce interleukin-10 (IL-10) in response to schistosome antigens and are less efficient in inducing T1D in SCID (severe combined immunodeficiency)–NOD mice, compared with T cells from non-infected NOD mice [9]. This suggests a role for IL-10 in helminth-induced suppression of diabetes. Soluble extracts from *Schistosoma mansoni* eggs increase the percentage of NKT cells and prevent diabetes in NOD mice [9]. Schistosomes contain a variety of cerebroside [10]. α -Galactosyl ceramide (α -GalCer), a member of the cerebroside family from the marine sponge *Agelas mauritanus*, is the most extensively studied ligand for CD1d and strongly activates NKT cells. Because α -GalCer prevents diabetes in NOD mice [11], it is tempting to

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speculate that the protection conferred by *S. mansoni* egg extracts is conferred by a similar mechanism.

Several reports suggest a protective role for pathogens in murine models of IBD [12,13]. IL-10 production is increased in the helminth-infected mouse. However, colonization of IL-10-deficient mice with lactobacilli or *Heligmosomoides polygyrus* attenuates the colitis that usually develops spontaneously [14,15], indicating that other immunological mechanisms are involved. This is supported by the negative results of clinical studies on IL-10 in Crohn's disease [16]. A recent publication by Elliot *et al.* shows that *Foxp3*⁺ T cells from *H. polygyrus*-infected *IL-10*^{-/-} mice transfer protection to naïve recipients [15], suggesting that CD25⁺ regulatory T (Tr) cells (characterized by expression of the transcription factor *Foxp3*) might mediate protection from IBD independently from IL-10.

The incidence and severity of experimental autoimmune encephalomyelitis (EAE), which is induced in mice by immunization with myelin antigens, can be slightly reduced by a pre-established infection with parasites or mycobacteria [17,18]. The reduction of EAE by helminth ova immunization is accompanied by an increase in IL-10 production, suggesting a role for IL-10 in helminth ova-mediated EAE reduction [19]. Finally, there are reports suggesting a protective role for pathogens in rodent models of arthritis [20].

The data outlined have led to the development of novel therapeutic intervention strategies aimed at reducing autoimmune responses in humans by using pathogens or commensals. Therapeutic BCG-vaccination is ineffective in patients with T1D [21,22]. A small study found reduced magnetic resonance imaging (MRI)-activity in BCG-immunized MS patients [23]. Probiotic bacteria reduced the incidence of pouchitis in a small study on patients with ulcerative colitis [24]. A small and uncontrolled clinical trial found the oral administration of *Trichuris suis* ova safe and possibly effective in Crohn's disease [25]; controlled trials are now underway. Furthermore, clinical trials for the treatment of autoimmune disorders using E5 62, a product secreted by filariae, are also planned.

Clearly, infections do not always protect from the development of autoimmunity. Autoimmune diseases sometimes occur shortly after infectious diseases. Classical examples are post-infectious encephalitis disseminata and rheumatic fever [1,2]. Antibiotic-resistant Lyme arthritis and spondylarthropathies develop after bacterial infections [26]. Another clear association exists between congenital rubella infection and T1D [1]. Finally, exacerbation of MS is 2–3 times more likely to occur during, or shortly after, common respiratory, gastrointestinal or urological infections [1,2].

Mice expressing a myelin-specific transgenic T-cell receptor (TCR) develop EAE spontaneously when kept in a conventional facility but not when they are kept under pathogen-free conditions. Similarly, HLA-B27 transgenic rats develop arthritis and bowel inflammation in conventional but not in germ-free conditions and analogous findings have been reported for mice susceptible to IBD [1,2].

Antigen-specific and antigen non-specific mechanisms have been proposed to explain the connection between

infection and autoimmunity. T-cell epitopes and inflammatory cytokines appear to have a role in infection-associated autoimmunity [2,27]. The molecular mimicry hypothesis is based on the finding that lymphocytes can recognize both microbial and self-antigens. It suggests that cross-reactive lymphocytes, activated by recognition of a microbial epitope, attack self-antigens with similar sequences and induce autoimmune disease [2,27]. Recently, several laboratories have used novel techniques, such as combinatorial peptide libraries and structural studies, to demonstrate that T-cell recognition of multiple different peptides occurs much more frequently than previously assumed and that sequence similarity is not a prerequisite for such cross-recognition [28]. Evidently, cross-reactivity between a particular microbial antigen and a particular self-antigen is not sufficient to induce autoimmune disease and despite decades of intense effort, no causal link has been proven between a particular infection and a particular autoimmune disease in patients [1,2,27,28].

Infection with the pancreatropic coxsackievirus B4 (CVB4) induces diabetes in mice transgenic for a TCR that recognizes a pancreatic self-antigen. Infection-induced inflammation and the release of sequestered antigens result in the activation of the transgenic autoreactive T cells and diabetes. Control experiments exclude cross-reactivity of the TCR with viral antigens ('molecular mimicry') [2,27]. Similarly, intracerebral injection of Theiler's virus into mice results in the presentation of myelin antigens that were previously hidden from the immune system, which then induces autoreactive T-cell responses against various myelin antigens [2,27]. The release of sequestered self-antigens can only explain the connection between infections and autoimmune diseases that affect the same tissue. The same is true for exaggerated immune responses against local infections that can cause chronic inflammation in the affected organ [29,30].

Microbial stimuli of innate immune cells, such as bacterial lipoproteins, double-stranded RNA, lipopolysaccharide (LPS) and CpG motifs, strongly activate the innate immune system, resulting in the enhanced expression of co-stimulatory molecules and cytokines by innate immune cells [31]. Type I interferon (IFN) and IL-15 can induce TCR-independent bystander proliferation of CD8⁺CD44^{hi} memory or effector T cells [32]. Similarly, antigen-experienced murine Th1 cells produce IFN- γ *in vitro* in response to a combination of IL-12 and IL-18 [33], and some human CD4⁺ memory cells are also activated by mixtures of cytokines, independently of TCR signaling [34]. Such cytokine-induced T-cell activation might well connect infection and autoimmunity and has been suspected as having a role in the pathogenesis of rheumatoid arthritis [35].

Antigen-independent mechanisms fit the clinical and epidemiological data on the connection between infection and autoimmunity better than antigen-specific mechanisms. Nevertheless, antigen-specific mechanisms must not be discarded. Survival and expansion of autoreactive Th cells can be supported either by recognition of self-antigen and overt autoimmune attacks or, clinically silent, by the recognition of cross-reactive microbial peptides. Once the

number of autoreactive T cells has reached a certain threshold, such as in patients who have already suffered previous episodes of autoimmune attacks, TCR-independent stimuli can trigger sufficient numbers of autoreactive effector T cells to cause autoimmune damage [2]. Figure 1 shows the possible mechanisms for how infections might modulate the development of autoimmunity.

Protection from, and induction of, allergic diseases by pathogen exposure: mechanisms and examples

Allergic immune responses to common environmental antigens lead to clinical disorders, such as allergic asthma, hay fever, eczema and allergic rhinitis. They are caused by allergen-specific responses initiated by CD4⁺ Th2-type cells. Th2 cells produce IL-4, IL-5, IL-9 and IL-13 after encountering allergen-derived peptides presented by antigen-presenting cells (APCs). These cytokines induce the development and recruitment of eosinophils, contraction of airway smooth muscle, production of allergen-specific IgE by B cells (leading to the degranulation of eosinophils and mast cells by IgE cross-linking) and mucus production, leading to airway hyper-reactivity

and, together with Th1 cells, to chronic allergic inflammation [3]. Paralleling the increasing prevalence of autoimmune disorders, there has also been a dramatic rise in the incidence and prevalence of allergic diseases within one generation. Although it is clear that the genetic pre-disposition is a prerequisite for the development of an allergy, environmental factors clearly have a role.

One factor associated with protection from allergic disorders is bacterial infection, in particular infection with mycobacteria. Infections with mycobacteria (in particular *Mycobacterium tuberculosis* and *Mycobacterium bovis*) strongly induce Th1 responses. Because IFN- γ has inhibitory effects on Th2 responses, many authors have speculated that infections with mycobacteria might protect humans from developing allergies. A report that a positive tuberculin test result was associated with a decreased risk of atopy and asthma in Japanese school-children supports this idea [36]. Most subsequent studies have failed to reproduce these findings [36]. Two recent publications, however, report that children vaccinated with BCG as neonates are protected from developing allergic disorders [37,38] and suggest that the age at BCG

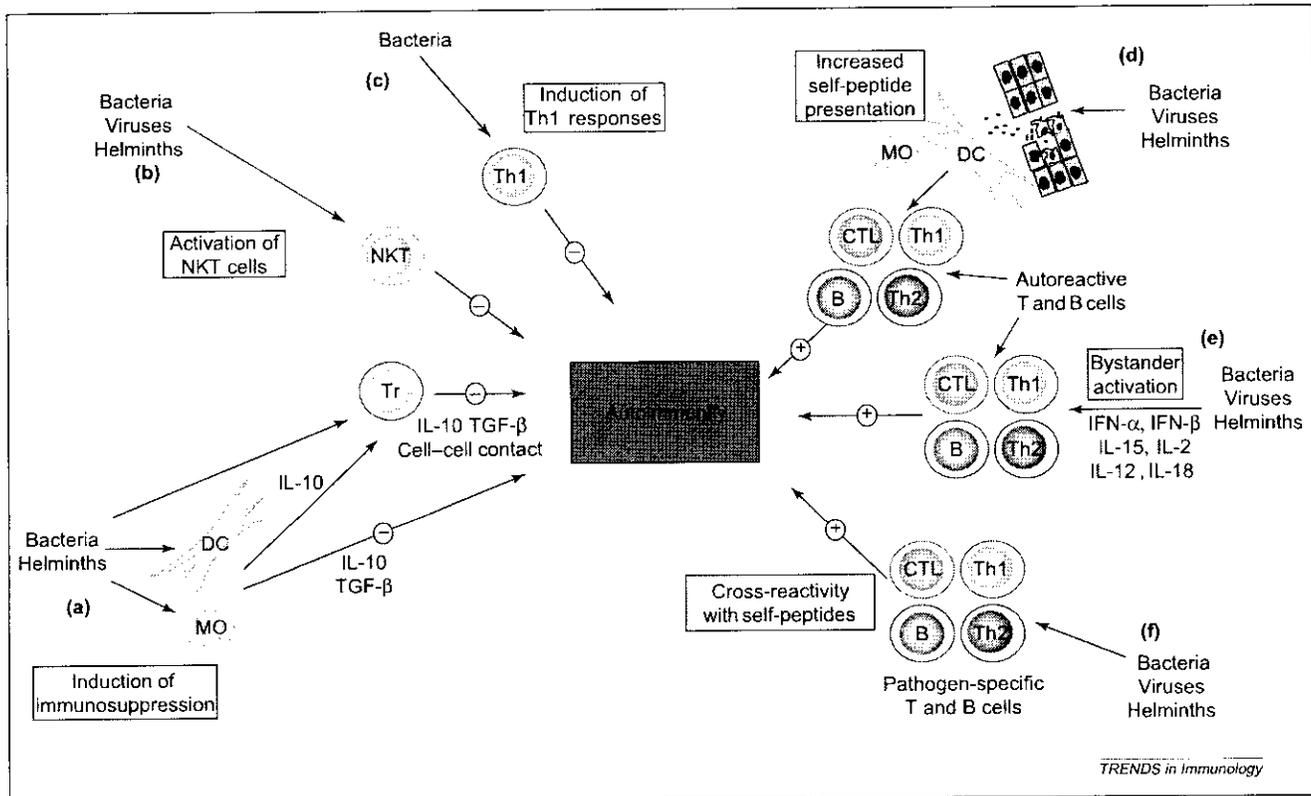


Figure 1. Potential mechanisms for how infections with pathogens might influence the development of autoimmunity. (a) Infections with helminths and bacteria induce the production of the immunosuppressive cytokines IL-10 and TGF- β , which both directly inhibit the development of autoimmune responses. Numbers of Tr cells are also increased by infections with bacteria and helminths, either by inducing the production of IL-10 by dendritic cells (DCs) or by other as yet undefined mechanisms. Tr cells suppress autoimmunity by inhibiting autoreactive T cell functions through a mechanism that involves cell-cell contact or by secreting IL-10 and TGF- β . (b) CD4⁺ NKT cells might also have a role in infection-mediated protection from autoimmune disease (by which mechanism is unclear). (c) Infections with bacteria induce profound CD4⁺ Th1 responses, which also suppress the development of autoimmunity by an as yet undefined mechanism. (d) Tissue destruction caused by bacteria, viruses or helminths increases the presentation of self-peptides by DCs or macrophages (MO). This might directly lead to the development or activation of pre-existing autoreactive Th1, Th2, CD8⁺ cytotoxic T lymphocytes (CTLs) or B cells, thereby causing or enhancing autoimmune disease. (e) A further mechanism of how infections might enhance or induce autoimmune responses is through bystander activation. During the normal immune response against the infectious agent, unactivated or tolerized autoreactive T and B cells might become activated by a TCR- or Ig receptor-independent mechanism. This effect can be mediated by the action of IL-2, IL-12, IL-15, IL-18, IFN- α or IFN- β . (f) Pathogen-specific Th1, Th2, B cells or CTLs might also crossreact with self-peptides, thereby causing or enhancing autoimmune disease. All of the mechanisms described probably have the greatest impact on autoimmune disease when the infection precedes the development of autoimmunity. However, they might all also have a role in the suppression or exacerbation of an already existing autoimmune disease.

vaccination might be important for protection. In addition, a lower prevalence of asthma is also found in Finnish women who had tuberculosis before the age of 20 [36]. Furthermore, BCG vaccination early in infancy might prevent the development of atopy in African children [36]. Numerous studies show that infection with live BCG or immunization with killed BCG prevents airway hyper-eosinophilia and the development of airway hyper-reactivity (AHR) and induces a partial reduction of allergen-specific IgE and IgG1 serum antibodies in mice, rats or guinea pigs [36]. A reduction in the levels of Th2 cytokines detected in draining lymph node and spleen cell cultures or bronchoalveolar lavages (BALs) is frequently associated with these findings. Furthermore, the effect is often associated with Th1 responses and is not observed in mice lacking IFN- γ , suggesting that mycobacteria exert their anti-allergy effects by inducing Th1 responses [36]. However, inhibition of allergen-induced airway inflammation by mycobacterial lipoglycan or killed *Mycobacterium vaccae* is associated with the increased production of IL-10 and not IFN- γ by T cells [36,39]. Furthermore, the application of antibodies against IL-10 and/or transforming growth factor- β (TGF- β) blocks the protective effects [36], indicating a Th1-independent mechanism. Supporting this view is a recent finding that *M. vaccae*-induced protection from allergen-induced AHR in mice is associated with the induction of CD11c⁺ cells that produce IL-10 and TGF- β [40]. In addition to mycobacteria, the exposure to other bacteria, such as *Chlamydia trachomatis*, *Listeria monocytogenes* or lactic acid bacteria, also suppresses the development of allergic responses [36,39,41,42].

There is also some evidence suggesting that infections with viruses protect against atopy development. A positive titer of anti-hepatitis-A antibodies correlates with a lower prevalence of allergies compared with hepatitis-A-negative controls [43]. Furthermore, depending on the time-point of infection, influenza A virus also decreases the development of airway eosinophilia after airway challenge with allergen [44,45] and also after respiratory syncytial virus (RSV) infection in mice pre-immunized with G-protein from RSV [46]. The anti-allergic effects of influenza A virus infection are associated with Th1 responses [44]. It is clear, however, that Th1 responses do not necessarily protect from allergy but can sometimes even exacerbate allergic responses [2].

Helminthic infections also seem to be associated with a lower incidence of atopic diseases [4]. In particular, infections with schistosomes or hookworms are associated with a reduced atopic phenotype [3,4]. In addition to these epidemiological associations, retrospective [3] and interventional studies [47] have shown that anti-helminthic chemotherapy results in increased levels of skin-test reactivity against common allergens. Infection of mice with *Strongyloides stercoralis* [48] or *Nippostrongylus brasiliensis* [49] suppresses pulmonary allergic responses. The reduction of allergen-induced airway eosinophilia and eotaxin production in *N. brasiliensis*-infected mice is IL-10 dependent [49]. Furthermore, treatment of mice, infected with *Heligmosomoides polygyrus* and allergen-challenged, with IL-10-neutralizing antibodies restores IgE titers and anaphylactic responses in a mouse model of food

allergy [50]. Interestingly, although infection of rats with *Strongyloides venezuelensis* induces AHR, the animals are protected from allergen-induced AHR after infection [51].

Clinical trials using live or dead pathogens, commensals or products derived from them, have been performed. Intradermal application of killed *M. vaccae* suspension results in some improvement in children with atopic dermatitis [52] but has no significant effects on the severity of asthma in adults [36,53]. Subcutaneous injection of live [36] but not heat-killed [54] BCG significantly improves the clinical symptoms of asthma in adults.

Lactobacillus rhamnosus, when given prenatally to mothers, decreases the incidence of atopic dermatitis in children at high risk [36]. Formulae containing *L. rhamnosus* or *Bifidobacterium lactis* improve atopic dermatitis in infants [55]. However, in adult patients with established asthma or food allergy, oral administration of *Lactobacilli* is ineffective [56]. A lipid A-containing vaccine causes weak, yet significant, improvements in pollinosis patients [57].

These findings clearly suggest that infections can protect from allergic disorders. However, numerous other publications indicate the opposite effect. In particular, respiratory viruses, such as rhinovirus (RV), RSV, influenza A and metapneumovirus, can exacerbate the symptoms of asthma in humans or can directly induce wheezing [3,58]. Additionally, RSV infections in the first year of life might be a risk factor for the development of childhood asthma [3]. In mouse models, viral infections can either exacerbate, or protect (see earlier) from, airway hyper-reactivity. RSV can directly induce airway eosinophilia and hyper-reactivity [3]. Low grade RSV infection, however, protects mice from allergen-induced inflammation in the airways [59], suggesting that the severity and frequency of an RSV infection might also be important in determining what effect the infection will have on the development of asthma. Influenza A virus induces increased airway responsiveness in allergen-exposed mice [3,44,60,61]. Depending on the timepoint of infection, however, influenza A could also protect from allergen-induced airway eosinophilia [44].

Several different mechanisms contribute to infection-induced exacerbation of allergic responses. Virus-specific IgE contributes to virus-induced asthma and cutaneous mast cell degranulation in mice [62]. Infections with respiratory viruses also increase airway eosinophilia in animals and humans [3]. RSV-mediated exacerbation of allergen-induced airway inflammation is partly mediated by IL-13 [63] and is associated with an increase in CCL5 [64]. Th1 cells can also exacerbate bronchial hyper-reactivity in mice [3,36] and both Th2 and Th1 responses to allergen are enhanced in influenza A virus-infected mice [60]. Some responses of innate immune cells to viral antigens contribute to enhanced allergic responses. The increased airway responsiveness in influenza-infected mice depends on pulmonary dendritic cells (DCs) [60,65]. RSV induces the production of IL-8 by lower-airway epithelial cells [3], thereby recruiting disease-enhancing neutrophils into the airways [66], and also induces IL-17, leading to increased mucus production in the airways [67].

In addition to viruses, some types of bacteria also appear to promote an allergic phenotype. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* can exacerbate asthma [68,69] or allergen-induced bronchial hyper-reactivity [70] and *Staphylococcus aureus* can trigger the exacerbation of atopic dermatitis. Exotoxins (superantigens) from *S. aureus* induce vigorous T-cell activation and cytokine release, thereby increasing the already established Th2 response in the skin [3]. A further bacterium possibly associated with increased allergic responses is *Bordetella pertussis* because infections with *B. pertussis* enhance allergic inflammation in the airways [71].

In contrast to most other types of infections, helminths induce strong Th2-type responses [4]. It seems therefore plausible that helminths promote allergic disorders by generally enhancing Th2-type inflammation. Supporting this view are the findings that infections with helminths can directly induce an asthma-like phenotype in mice and rats [3] or can lead to the breakdown of oral tolerance against allergen [72]. Allergic symptoms occur more often in children seropositive for *Toxocara* or *Ascaris* species than in seronegative children and anti-helminthic treatment ameliorates asthma [3,4]. Chronic helminth infections or the exposure to helminth-derived products have also been linked to urticaria [73]. Severe allergic reactions

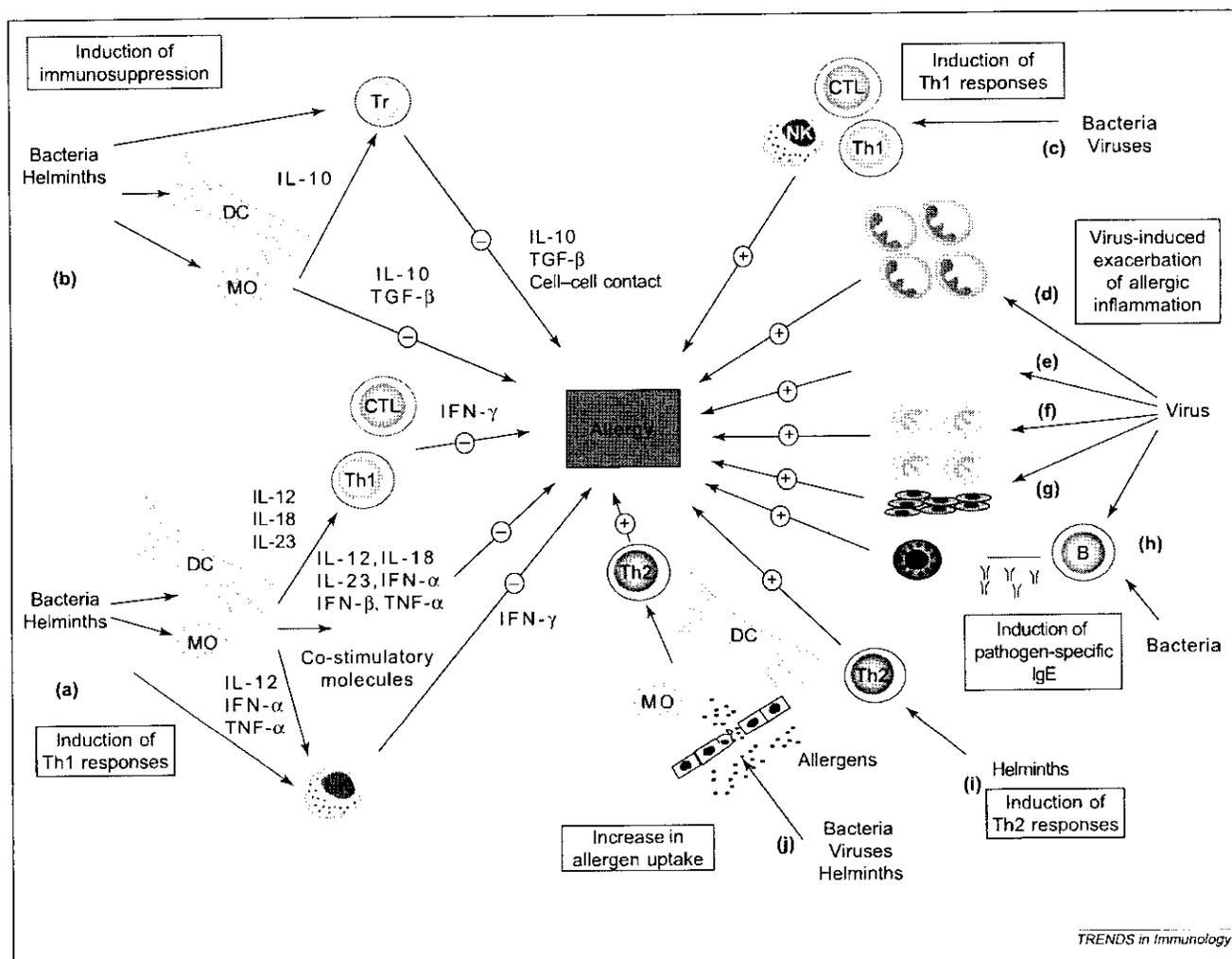


Figure 2. Potential mechanisms for how infections with pathogens might influence the development of allergic diseases. (a) Infections with viruses or bacteria induce Th1 responses. The IFN- γ produced by CD4⁺ Th1 cells, NK cells or cytotoxic CD8⁺ T lymphocytes (CTLs) directly interferes with the development of Th2 cells. Viral and bacterial infections also induce the production of the Th2 response inhibiting cytokines IL-12, IL-18, IL-23, TNF- α , IFN- α and IFN- β by DCs and macrophages (MO). (b) MO, and in particular DCs, also express certain co-stimulatory molecules known to be associated with enhanced Th1 and decreased Th2 responses, thereby further reducing Th2-cell development. Infections with helminths and bacteria induce the production of IL-10 and TGF- β , which both directly suppress the development of allergic responses. Tr-cell numbers are also increased by infections with bacteria and helminths. Tr cells suppress allergic responses by inhibiting Th2 effector functions, by cell-cell contact or by secreting IL-10 and TGF- β . (c) Th1 responses induced by viruses or bacteria directly exacerbate allergic diseases by generally increasing the inflammation in the affected tissue. Respiratory viruses can directly induce (d) airway eosinophilia, (e) goblet cell metaplasia and mucus production, (f) airway neutrophilia or (g) smooth muscle contraction, directly causing wheezing or enhancing already existing allergic inflammation. (h) Viral- or bacterial-specific IgE mediates mast cell degranulation during infection or re-exposure to the pathogen, enhancing a pre-existing allergic response or directly causing it. (i) Infections with helminths induce profound Th2 responses that can enhance allergic responses. (j) Infections might also cause damage to the natural protective barriers, which normally limit the access of allergens to the body, leading to the development of allergen-specific Th2 cells or enhance allergic responses by, for example, increasing mast cell degranulation. The mechanisms shown in a, b and d-j probably have their strongest suppressive or inducing effect on allergic disorders at a young age when allergic responses have not yet developed. Most mechanisms also have a role in inhibiting (b) or exacerbating (c-j) already pre-existing allergic responses.

following ingestion of fish contaminated with *Anisakis simplex* have also been reported [74]. Figure 2 shows the potential mechanisms of how infections influence the development of allergic disorders.

Common themes

The scientific evidence presented here clearly shows that infections have multiple and seemingly opposing effects on both autoimmune and allergic diseases. For example, there are numerous types of infections that impact on atopy but not on autoimmunity and visa versa (Table 1). However, there are also similarities. Helminths and mycobacteria seem to be particularly good at protection and the timepoint (infections before the onset of atopy or autoimmunity have the greatest impact), age at infection, route, localization and dose of the infection all have a role. Furthermore, prevention seems to be more easily accomplished than cure. The innate immune system also appears to be important in infection-induced modulation of autoimmunity and atopy. DCs, macrophages, mast cells and NK cells are the first cells that encounter an invading pathogen, taking up and responding to self- or foreign-proteins (allergens), thereby initiating and instructing the following adaptive immune responses, which result in the

Table 1. Examples of infectious diseases that might have an impact on the development of autoimmunity and/or allergic disorders

Type of Infection	Protection	Exacerbation or induction
Effects of infection on autoimmune diseases		
Bacteria	BCG [7,18,23] Lactobacilli species [14]	Borellia species [26,27] <i>Mycobacterium tuberculosis</i> [1,2,20] Probiotic bacteria or commensals [1,2]
	<i>M. tuberculosis</i> [7] Probiotic bacteria or commensals [20,24] <i>Salmonella typhimurium</i> [8]	
Virus		Theilers virus [2,27] Coxsackie virus [27] Rubella virus [1,27]
Parasites	<i>Hymenolepis diminuta</i> [12] <i>Heligmosomoides polygyrus</i> [15] <i>Schistosoma mansoni</i> [9,11,13,17,19] <i>Trichuris suis</i> [25,77]	
Effects of infection on allergic disorders		
Bacteria	BCG [36,38] <i>Bifidobacterium lactis</i> [55]	<i>Bordetella pertussis</i> [71] <i>Chlamydia pneumoniae</i> [69] <i>Mycoplasma pneumoniae</i> [68-70] <i>Staphylococcus aureus</i> [3]
	<i>Chlamydia trachomatis</i> [41] Lactic acid bacteria [42] <i>Lactobacillus rhamnosus</i> [55] <i>Listeria monocytogenes</i> [3,36] <i>Mycobacterium tuberculosis</i> [36] <i>Mycobacterium vaccae</i> [36,39,40,52]	
Virus	Hepatitis A virus [43]	Influenza A virus [3,44,60,61,65] Metapneumovirus [58] Rhinovirus [3] RSV [3,63,64,66,67]
	Influenza A virus [44,45] RSV [46,59]	
Parasites	<i>Heligmosomoides polygyrus</i> [50] Hookworm species [47] <i>Nippostrongylus brasiliensis</i> [49] <i>Schistosoma haematobium</i> [4,47]	<i>Anisakis simplex</i> [74] Ascaris species [3,4] <i>Fasciola hepatica</i> [73] <i>Nippostrongylus brasiliensis</i> [3] <i>Strongyloides venezuelensis</i> [51] Toxocara species [3,4]
	<i>Strongyloides stercoralis</i> [48] <i>Strongyloides venezuelensis</i> [51]	

induction and exacerbation or inhibition of both autoimmunity and allergy.

There are also some common mechanisms for how infections might mediate their effects on both types of disease. (i) Bystander activation of CD8⁺ or CD4⁺ T cells by infection might lead to, or exacerbate, autoimmunity and atopy. (ii) Infection-induced tissue damage might lead to increased self-peptide presented by APCs or increased penetration or uptake of allergens in the lung or gut, thereby inducing or exacerbating autoimmunity or atopy. (iii) The immune response against the pathogen itself might cause autoimmunity or allergic disorders. Allergic disorders might be directly caused by IgE, which is specific for viruses or bacteria, during chronic infection or re-infection. (iv) Autoimmunity, and in particular atopy, can be inhibited by infections that induce Th1 responses. (v) Tr cells, induced by (chronic) infection, appear to be one of the most important cell types for suppressing both autoimmunity and atopy.

Conclusions and implications

Taken together, it is clear that under certain circumstances some infections can inhibit, induce or exacerbate allergic or autoimmune diseases (Table 1). There are several, not mutually exclusive, hypotheses on how infections exert their influence. The current, most popular, hypothesis on how infections inhibit the development of both types of disease, suggests that microbial molecules trigger certain programs, such as IL-10 production by DCs, which thereupon instruct the development of Tr cells [40,75,76]. Increasing evidence for this hypothesis is currently being published; nevertheless, it is far from proven and other mechanisms might contribute to infection-mediated protection.

How can we make use of the knowledge that infections protect from allergies and autoimmunity? Considering the overwhelming morbidity and mortality associated with infectious diseases, including some of those that seem to have a positive influence on allergy and autoimmunity, one certainly does not want to go back to the not-too-distant past when children frequently died of infectious diseases and the average life expectancy was only forty years. Nevertheless, the immune system seems to benefit from regular encounters with some microbes, possibly opening a new window for therapeutic intervention in autoimmunity and atopy. The first clinical trials show some promising results [23,24,36,52,55,57,77], however, complete suppression of atopy and autoimmunity could come at a cost. The therapeutic application of pathogens or molecules derived from them might be burdened with clinically relevant immunosuppression and possibly an enhanced risk of developing cancer [78]. The selective induction of Tr cells specific for allergen or self-peptides (relevant for autoimmune disease) might overcome this prospective problem.

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Debate

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The asthma epidemic and our artificial habitats

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Abstract

Background: The recent increase in childhood asthma has been a puzzling one. Recent views focus on the role of infection in the education of the immune system of young children. However, this so called hygiene hypothesis fails to answer some important questions about the current trends in asthma or to account for environmental influences that bear little relation to infection.

Discussion: The multi-factorial nature of asthma, reflecting the different ways we tend to interact with our environment, mandates that we look at the asthma epidemic from a broader perspective. Seemingly modern affluent lifestyles are placing us increasingly in static, artificial, microenvironments very different from the conditions prevailed for most part of our evolution and shaped our organisms. Changes that occurred during the second half of the 20th century in industrialized nations with the spread of central heating/conditioning, building insulation, hygiene, TV/PC/games, manufactured food, indoor entertainment, cars, medical care, and sedentary lifestyles all seem to be depriving our children from the essential inputs needed to develop normal airway function (resistance). Asthma according to this view is a manifestation of our respiratory maladaptation to modern lifestyles, or in other words to our increasingly artificial habitats. The basis of the artificial habitat notion may lie in reduced exposure of innate immunity to a variety of environmental stimuli, infectious and non-infectious, leading to reduced formulation of regulatory cells/cytokines as well as inscribed regulatory pathways. This could contribute to a faulty checking mechanism of non-functional Th2 (and likely Th1) responses, resulting in asthma and other immuno-dysregulation disorders.

Summary: In this piece I discuss the artificial habitat concept, its correspondence with epidemiological data of asthma and allergy, and provide possible immunological underpinning for it from an evolutionary perspective of health and disease.

Background

Asthma is a major health problem that has reached alarming proportions in the past two decades in western societies [1]. What lies behind the recent increase in asthma in affluent societies is still an area of lively debate, but its rapid changing patterns and huge variation across populations favor environmental explanations [1-3]. While

assessment of different old and new exposures is continuing, a unifying paradigm remains elusive, so as a guiding principle for prevention. The simultaneous increase of all forms of allergic disease on the other hand, argues for a change in host susceptibility/resistance [4].

The apparent association between asthma and western lifestyle has led to numerous studies trying to link novel or increased exposures associated with westernization-modernization, especially those occurring during childhood, to asthma. For example, exposure to gas cooking, tobacco smoke, trans fatty acids, domestic animals, and allergens were found to influence respiratory health, but did not provide a conclusive answer to the current trends in asthma [5-10]. While it is early to discard the role of these and other factors, a major contribution of asthma research during the past two decades lies in the elucidation of its heterogeneous and multi-factorial nature, where different exposures have different roles and relevance depending on the target population, setting, and disease course.

Discussion

1- The hygiene hypothesis and asthma

Since its introduction in the nineties, the hygiene hypothesis (HH) continues to generate enthusiasm among asthma researchers as the most comprehensive theoretical framework, by which the relation between suspected environmental factors and allergy can be tested [11-13]. This hypothesis originated from the coupling of observations on the allergy-protective effect of sibship size/birth-order with the emerging concept of helper T cell polarization into two counter-regulatory subsets; pro-infection Th1, and pro-allergy Th2 [14,15]. Backed by some experimental and clinical evidence [16-18], the hygiene hypothesis suggests that the recent rise in allergic disease among children in affluent societies is due the preferential programming of the T cell repertoire towards pro-allergy Th2 responses, brought by the decline in infections (increased hygiene, immunization, decreased sibship size, antibiotic use) [13-15]. With the increasing recognition of the role of T regulatory cells (Tregs) and cytokines in the pathogenesis of allergic inflammation, the hygiene paradigm has been extended recently integrating infection's role in generating such cells and mediators [19-21].

Asthma trends however, did not fit well with the hygiene model, which failed to explain the urban predominance of asthma, the increase in non-allergic asthma, the disparity between atopy and allergy in some populations, and the asthma inducing properties of some infections [22-27]. Specifically, studies looking at the infection-asthma relationship failed to yield a consistent pattern so far [28-34], prompting David Strachan, the father of the hygiene hypothesis, to conclude that "the totality of current evidence from cross sectional and longitudinal studies of common specific and non-specific infectious illnesses in infancy and childhood offers no support for the hygiene hypothesis" [11]. Other studies doubted even the fundamentals of the HH showing that the effect of siblings is not universal, or could have been programmed in utero

rather than being a marker of childhood infection [35,36]. Perhaps the hygiene model's major shortcoming lies in its concentration on only one aspect (infection) of the drastic change that touched upon every detail of life in western societies in the past few decades. It also adopted a mechanistic approach for the study of adaptive immune responses and the relation between exposure-outcome, where an array of potential interactions are reduced to a single level; Th1-Th2 counter-regulation, siblings-infection, daycare attendance-infection, dog ownership-endotoxin, farming-endotoxin, etc. In brief, the search for a holy grail in the asthma epidemic may need to be replaced by the conceptualization of a more generalizing notion that allows for the consideration of multitude of factors within an ever changing environment.

2- Asthma and our artificial habitats

The hygiene model on the other hand, involved an evolutionary logic alerting us to the negative potential of sudden elimination of exposures that have shaped throughout the ages our organs and systems [37]. Health from such perspective is not about abstract assessment of the relation between exposure and outcome, or eliminating harmful exposures, but about seeing the whole dynamics of our interaction with our novel habitats [38]. Because of the slowness of adaptive evolutionary machinery, of particular interest according to this perspective are lifestyle factors that either witnessed a rapid change in recent times or represent an obvious departure from the conditions prevailed for most part of our evolution, i.e. factors likely to exemplify the discordance between our "Stone Age" genes and "Space Age" living conditions [37,38].

General trends of asthma show that populations who conserved elements of ancient lifestyles have low levels of asthma. The north-south, urban rural, gradients in asthma occurrence have been extensively documented [24,37,39-43]. In additions, studies in Africa show that some populations seem to be protected from asthma regardless of atopic predisposition or parasitic infection (both are Th2-related) [20,22,44-46]. This indicates that some environmental influences associated with more traditional lifestyles are conferring respiratory resistance to stimuli that could have lead otherwise to clinically relevant airway inflammation. Within western societies furthermore, lower levels of asthma were found in families with traditional lifestyles [47,48] and higher levels of asthma were found among obese or less physically fit children and adults [49-51]. Because not all these observations can be explained by variability in infection, or any other single factor for that matter, a broader concept seems more plausible.

Modern life is increasingly placing us in static, artificial, micro-niches optimized for our convenience, but which bear little resemblance to the dynamic inputs provided by the environments that nurtured our evolution. In other words, we are increasingly living within an array of artificial habitats designed to handle us very well, but we may well not be equipped to handle them. Asthma according to this view, becomes a manifestation of our respiratory maladaptation to modern lifestyles. Changes that occurred during the second half of the 20th century in industrialized countries with the spread of central heating/conditioning, building insulation, hygiene, TV/PC/games, manufactured food, indoor entertainment, cars, medical care, and sedentary lifestyles all seem to be depriving our children from the essential inputs needed to develop normal airway function (resistance).

3- Epidemiology of asthma from a new perspective

The suggested view -called here the artificial habitat (AH)- can provide alternative interpretations to existing data starting with the protective effect of sibship size/birth-order, which is one of the landmark observations of the HH that has been ascribed to increased exposure to infection [52]. It can be postulated that the mechanism of protection of siblings (especially older males) is related to their importance to the child's level of physical activity as well as ability to spend more time outdoors (i.e. in a more dynamic environment). This is particularly relevant to children living in dangerous neighborhoods, such as inner cities in the US, where the spread of asthma represents one of the main challenges to the hygiene paradigm [53]. Indeed, Andrew-Aligne and colleagues found that the higher prevalence of asthma among inner city black children is not due to race or low income per se, but to their living in an urban setting [54]. Additional intriguing support to the AH notion comes from the two largest studies looking at the effect siblings on the occurrence of allergy, whereby a stronger protective effect was observed for brothers than for sisters [55,56]. While exposure to infection cannot be expected to be related to sibling's gender, activity and outdoor time may well be influenced by this factor. By the same token, birth order can determine, among other things (e.g. social development, healthy food availability), the child's level of activity (how many playmates the child have) and ability to spend time outdoors. As new evidence are emerging against the HH's assumption considering the infection-related effect of the sibship size/birth-order, by showing for example that the role of birth order is independent of sibship size [57], and that in the same population sibship size can protect against asthma while infection predispose to it [31,58], the AH concept seems to offer an alternative explanation.

Another important observation of the hygiene paradigm concerns the protective effect of early daycare attendance

on later development of asthma, which is ascribed to increased exposure to infection [28]. Alternatively, it can be argued that the daily routine at a daycare center would be different in many aspects from home, in addition to exposure to infection. Reducing potential differences in activity, exposure, socio-behavioral development, and parental attitudes between those who do and don't attend daycare to mere infection seems over-simplistic. The AH concept looks at this observation from a broader angle involving a mixture of lifestyle and developmental factors. Related to this issue is the argued window of opportunity in early infancy for the protective effect of daycare attendance/infection [59,60], which is connected to a critical period of immune education [13]. By its own nature in contrast, the AH view is consistent with the notion that environmental signals throughout the lifespan can affect the risk as well as the course of asthma and allergy.

On a different juncture of asthma research, a multitude of recently published reports show lower rates of asthma and atopy in children raised on a farm [61-68]. Heavily influenced by the HH, these observations were largely attributed to increased exposure to bacterial components found in barns or farm milk (endotoxin in particular) [67-69], forgoing that children raised on a farm have very different lifestyles from children growing in inner cities in the US for example, where infection is also commonplace [70]. For example, one of the landmark farming studies has shown that endotoxin levels in children's mattresses were inversely associated with the occurrence of hay fever and atopic asthma [67]. However, leukocytes of children exposed to high levels of endotoxin produces less Th2 suppressing cytokines (mainly interleukin 10), arguing against the endotoxin-hygiene paradigm [67,71,72]. From the AH perspective however, a farm is the closest we can get in today's' western societies to conditions prevailed for most part of our evolution. Such an environment can provide ample opportunities of behaviors and exposures different from those of modern urban life.

The AH perspective is consistent with the assumption that time spent outdoors and level of physical activity should be protective against the development of asthma. A recent study by McConnell and colleagues however, has shown just the opposite, where the risk of developing asthma was positively associated with number of sports played and time spent outdoors [73]. However, when participating communities were separated according to their level of atmospheric ozone, this association was only seen in the high ozone levels communities, while number of sports played and time spent outdoors seem to be protective in the low ozone communities [73]. On the other hand, twines in the Odense study who participated in conditioning exercise had a decreased risk of asthma compared to the more sedentary co-twins [51]. The physiological

underpinning of the effect of activity on asthma can be partly elucidated by the work of Feldberg and colleagues and Togiias and colleagues, who showed that disruption of dynamic breathing (static breathing without deep breaths or sighing) can lead to bronchial hyper-responsiveness (BHR), the pathophysiological hallmark of asthma [74,75]. Furthermore, recent evidence shows that obesity and weight gain are associated with increased risk of BHR [76], providing more insight on possible ways by which sedentary life factors can co-interact to predispose to asthma.

Finally, the AH concept can offer an explanation for some puzzling observations, such as the protective effect of dog ownership on asthma [77,78]. While the HH proponents looked for explanation in endotoxin levels associated with dog ownership, but with conflicting results so far [79], one can argue that the change in lifestyle (of children particularly) associated with dog ownership can be responsible (more playing, more time out, emotional interaction, as well as exposure to dog's constituents). Generally, families who opt to have a dog may be different from those who don't in being more active and outgoing. The focus here on activity and outdoor time is because these factors are clearly envisioned. Other aspects of traditional lifestyles may be just as important, such as household air exchange (e.g. affecting allergens, pollutants, humidity), nutritional habits (e.g. breast feeding), as well behavioral adaptations.

4- An innate control of asthma and allergy

Now how can the AH view be related to what we know about the immunopathology of asthma and allergy? Asthma is an immunological disorder with a predominant Th2 inflammatory response in the airways. This Th2 response is thought to be a remnant of our ability to expel parasites abundant in the cradle of human evolution, the tropical savannah [80]. Indeed, evidence exist showing that Th2 pro-inflammatory genetic alleles are more prevalent in populations with a tropical origin than those with a temperate one [81]. It is possible that the need to deal with a wide variety of pathogens may have meant that the activation threshold of Th2 responses has to be set low, leading to many false alarms to non-pathogenic particles and giving rise to asthma. Evolutionary logic indicates however, that a trait with a potential to endanger air passage into our vital respiratory organs would not have been selected, had some regulatory mechanisms not been in place. Studies on the initial phase of allergic sensitization show that a transient low-level IgE (the atopic antibody) response to inhalant antigen occurs in normal children, with those who do not develop allergy down-regulate it in the first years of life [82-84]. Asthma in this regard, becomes a manifestation of breakdown of regulatory mechanisms at respiratory mucosal surfaces.

But let's take one step back to look at another recent puzzling trend; the increase of Th1 autoimmune disorders such as type-1 diabetes and multiple sclerosis in western societies [21]. Recent evidence suggests that that the two groups (Th1 and Th2 mediated diseases) can be associated in individuals [85-88], arguing against the Th1-Th2 counter-suppression of the HH, and favoring a common ground of faulty regulation. Such developments were picked up by proponents of the HH to suggest that hygiene can work through depriving the immune system from signals necessary for the development of regulatory pathways/cells capable of dampening both Th1 and Th2 responses [89,90]. While this can be true, the focus on infection yet again is a reductionistic view likely to suffer the same shortcomings of the original Th1-Th2 counter-regulation of the HH. At the same time, advances made in immunology were unraveling the central role of the innate immune system in orchestrating immune responses [91]. In particular, antigen presenting cells, such as dendritic cells (DCs), can engage infectious components with their Toll-like receptors (TLRs) (a group of ancient immune recognition molecules) leading to activation of adaptive immune responses and induction of regulatory cells and mediators [92,93]. In their turn, T regulatory cells (Tregs), which are induced naturally or by elements of innate immunity are able to regulate all types of adaptive immune responses as well as influence DCs activation and regulation [94,95]. Interestingly, it looks that none of the Th1, Th2, or Treg-inducing functions of DCs is an intrinsic attribute that is not sensitive to instructions from the surrounding environment [96,97]. Without getting into the details of this fascinating and still unfolding field, the move from the see/saw mechanistic counter-regulation of adaptive Th1-Th2 responses to elements of innate immunity offers an evolutionary sound and possibly robust checking mechanism (break) against inappropriate responses (e.g. Th2 responses to non-pathogenic elements) at our vital airways. The ability of DCs to be activated in response to danger signals induced by stress, damage, or necrotic cell death [98], and the role of DCs at the gastrointestinal tract in the development of mucosal tolerance [99], broadens their possible range of involvement with different environmental stimuli and thus their contribution to immune homeostasis at the respiratory surface. For example, heat-shock proteins (hsps, which are highly conserved cellular proteins that can be produced by thermal stimuli, physical activity, or other stresses) can activate DCs as well as contribute to T cell regulation of inflammatory responses [100,101].

Taken together, it can be suggested according to the AH concept that dynamic/traditional lifestyles with associated exposures can ensure constant challenge of DCs and other elements of innate immunity giving rise to immune responses, but at the same time maintaining adequate

turnover of regulatory cells and cytokines and inscribed regulatory pathways. This ongoing activation of regulatory pathways can help maintain healthy control of non-functional Th2 responses at the respiratory surface. The DC-orchestrated dynamic balance between Th2 responses and regulatory mechanisms is likely to influence all phases (initiation, effector) of inflammation in the airways, and throughout the lifespan of the individual.

Summary

While it offers no specific explanation to different asthma trends and variations, the suggested AH notion provides a generalizing scheme for the study of asthma, and provides novel insights for existing epidemiological observations. According to this perspective there is no single answer to the asthma epidemic, but different factors have different relevance depending on the population and environment in focus. In addition to being free from the HH one-dimensional approach for the relation between exposure-outcome, this view is evolutionary-driven allowing to place the asthma epidemic within the wider perspective of increasing discordance between us and our dramatically changing environments. Sedentary lifestyles, static indoor microenvironments, and automation of the food chain are apparently not only predisposing us to obesity and cardiovascular disease but also depriving our respiratory system from many stimuli necessary for the development of normal airway resistance. The immunological basis of the AH notion can lie in the centrality of innate immunity and its ability to respond to different types of environmental stimuli, insuring adequate turnover of regulatory cells and mediators. The evolutionary tenet "the more we change the world the more we stay the same" probably lacks accuracy. Newer environments, constantly confront us with new adaptive challenges that should be looked upon, as in the case of asthma, within the evolutionary context of health and disease.

Abbreviations

HH- hygiene hypothesis

AH- artificial habitat

DCs- dendritic cells

BHR- bronchial hyper-responsiveness

IL10- interleukin 10

hsp- heat shock proteins

Th1- T helper cell type 1

Th2- T helper cell type 2

Tregs- regulatory T cells

IgE- immunoglobulin E

TLRs- Toll-like receptors

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

Dr. Wasim Maziak is the sole author and contributor to this manuscript.

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