The influence of infections on the development and severity of allergic disorders

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The frequency and severity of atopic disorders are steadily increasing, particularly in developing countries. The reason for this observation is not clear. Recent studies indicate that infections with viruses and especially with bacteria early in life may help to inhibit allergic Th2 responses by skewing the immune system towards Th1 responses. However, infections can also lead to the exacerbation of atopic disorders.

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Abbreviations

APC	antigen-presenting cell
DC	dendritic cell
LPS	lipopolysaccharide
MBP	major basic protein
OVA	ovalbumin
RSV	respiratory syncytial virus
RV	rhinovirus
SA	superantigen

Introduction

It is well established that genetic and environmental factors contribute to the onset and maintenance of allergic diseases such as bronchial asthma and atopic dermatitis. Since the natural mutation rate is low, altered environmental/ lifestyle conditions are thought to be responsible for the increasing prevalence and incidence of allergic diseases. Epidemiological and clinical studies have provided compelling evidence that suggests a link between the relative lack of infectious diseases and the increase in allergic disorders (reviewed in [1]); this is referred to as the 'hygiene hypothesis'. According to this theory, viral and bacterial infections prevent the induction of allergen-specific Th2 cells because they establish Th1-biased immunity. In particular, the prenatal period and early childhood are considered to be critical intervals for the establishment of the Th1/Th2 balance. On the other hand, several studies have suggested that viral/bacterial infections exacerbate allergic diseases, for example bronchial asthma, airway hyper-responsiveness and atopic dermatitis. Therefore, viral/microbial infections and/or their products may have bidirectional effects on the development of allergy and asthma.

This review will focus on recent findings relating to the interaction between allergic disorders and infectious diseases, with the main emphasis on viral and bacterial infections. At various points of this review, the reader will be referred to more detailed reviews on previous advances in the field and specific areas of immunological research that we touch upon.

The influence of viral infections on the development and severity of allergic disorders

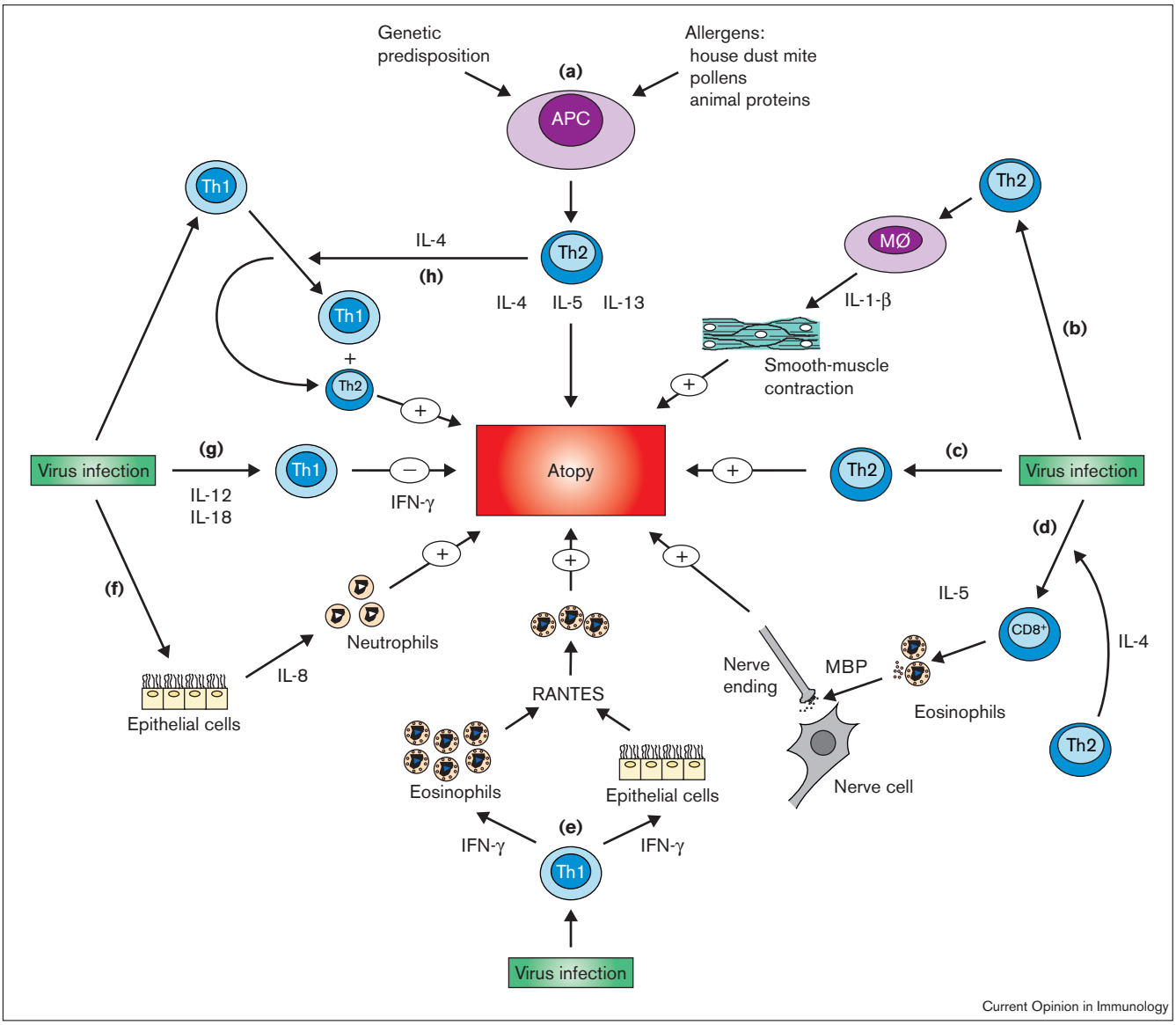
Do viral infections inhibit the development of atopic disorders?

The immune response induced by viral infections is generally characterized by the activation of NK cells and $CD8^+$ and $CD4^+$ T cells secreting IFN-γ via MHC-class-I- and class-II-restricted antigen presentation by professional antigen-presenting cells (APCs). Since IFN-γ has the potential to inhibit the development of Th2 responses, it is plausible that viral infections early in childhood could lead to a decrease in the atopic phenotype later in life.

Up to now very few data supporting this hypothesis have been published. Studies on the effects of measles vaccination on children in Guinea-Bissau have shown that children who were not vaccinated against measles were significantly less likely to develop allergic disorders than their counterparts who had been vaccinated [2]. One of the interpretations provided by this study was that infection with the measles virus might be protective against atopy. However, a recent report by Paunio *et al.* [3] found that children who had been infected with measles (but had cleared the infection) also had a higher frequency of atopy in comparison with children who did not have a measles infection (these children had been vaccinated and exposed). Furthermore, Imani *et al.* [4] demonstrated that a human B cell tumor line treated with IL-4 and infected with measles virus exhibited an increase in IgE class-switching in comparison with control cells treated only with IL-4. This suggests a mechanism by which measles virus may increase the production of IgE during measles virus infection in humans.

Other viruses whose presence has been negatively correlated with the prevalence of atopy are hepatitis A virus and adenovirus. Matricardi *et al.* [5] showed that military students in Italy who had a positive titre of anti-hepatitis-A antibodies showed fewer signs of allergic manifestations as compared with hepatitis-A-negative students. This suggests that hepatitis A virus infection somehow protected from the development of atopy. However, the majority of vaccine adjuvants in use today are known to induce a Th2-type response by increasing the production of Th2-type

Figure 1



The possible influence of viral infections on the development of atopic disorders. **(a)** Genetic factors and environmental allergens determine whether allergen-specific Th2 cells are generated, leading to the development of atopy. Virus infection may have a variety of effects and, for simplicity, these are shown emanating from the right, lower centre and left of the figure. **(b)** IL-1-β produced by macrophages (MØs) after infection by RV leads to increased airway smooth-muscle contraction, resulting in increased airway reactivity. **(c)** Infections with RSV or parainfluenza directly induce Th2 responses, leading to the exacerbation of allergic disorders. **(d)** IL-4 produced by allergen-specific Th2 cells switches virus-specfic Th1 cells to a Th2 type. These virus-specific $CD8^+$ T cells secreting IL-5 recruit eosinophils into the vicinity of nerve cells, where the eosinophils degranulate and release MBP; this interacts with M2 muscarinic receptors on airway parasympathetic nerves, inhibiting the suppression of acetylcholine release and resulting in increased airway reactivity. **(e)** The secretion of IFN-γ by Th1 cells after virus infection induces the production of RANTES by eosinophils and airway epithelial cells, thereby increasing the influx of eosinophils. **(f)** RSV and RV infections induce the production of IL-8 by lower-airway epithelial cells, attracting neutrophils into the airways and further increasing inflammatory responses at this site. **(g)** Viral infections that induce strong Th1 responses inhibit the development of allergen-specific Th2 cells through the production of IFN-γ (by Th1 or NK cells), IL-12 (by MØs or DCs) and IL-18 (by MØs and Th1 cells) at the site of naive T cell priming. **(h)** The IL-4 secreted during the allergic Th2 response deviates the normally Th1-dominated antiviral immune response towards a Th2 response and further exacerbates the allergic reaction.

cytokines and IgE antibodies [6–8] thereby potentially elevating the predisposition towards atopy in vaccinated persons, compared with infected persons. The observation of Stampfli *et al.* [9], that an intramuscular infection of mice with a replication-deficient adenovirus inhibited allergic airway-inflammation, supports the idea that viral infections may under certain conditions reduce an allergic phenotype. This view is supported by the demonstration that influenza A virus infection decreased the development of airway eosinophilia after airway challenge with allergen (K Erb,

H Moll, unpublished data) and after respiratory syncytial virus (RSV) infection in mice preimmunized with G-protein from RSV (T Hussel, personal communication).

Taken together, however, caution should be taken in arriving at the conclusion that viral infections have a protective influence against atopy. Further experimental and epidemiological data are needed to clearly establish if, and under which conditions, viral infections may decrease the development of atopy both in animal models and humans.

Virus-induced exacerbation of allergic disorders

Although there is no clear evidence suggesting that viral infections in general may induce allergic disorders, there is little doubt that a number of respiratory viruses can exacerbate the symptoms of asthma in humans. The most common form of virally exacerbated asthma in humans is induced by rhinovirus (RV). Furthermore, this effect has recently been observed using influenza A virus and RSV in experimental animal models. Suzuki *et al.* [10] reported that an infection with influenza A virus leads to an increase in airway responsiveness and allergen-specific IgE production in aerosolized, antigen-exposed mice. An increase in ovalbumin (OVA)-specific IgG_1 antibodies, leading to anaphylactic shock, was also reported when OVA-induced airway sensitization was combined with influenza A virus or RSV infection in mice [11]. In addition, infections with RSV were found to increase allergen-induced airway hyper-reactivity in mice [12]. Furthermore, it was reported that RSV infections can directly (independently from an underlying allergic disorder) induce airway eosinophilia and hyper-reactivity, with the effect being dependent upon $CD8^+$ T cells [13]. Moreover, the observation that parainfluenza infection of guinea pigs induced airway eosinophilia and eotaxin secretion in the lung [14] suggests that the immune response towards viruses may have a stronger Th2 compartment than previously suspected.

These observations suggest that viruses, in particular RSV infections, may generally lead to increased airway reactivity after allergen exposure. However, this effect was not observed in guinea pigs [15]. Epidemiological studies in humans also suggest a link between RSV infection and asthma. Sigurs *et al.* [16] reported that RSV infections in the first year of life might be a risk factor for the development of asthma later in life. However, a recent longitudinal study on children infected with RSV in early life suggests that RSV infection in the lower airways does not induce atopic asthma, since nearly all wheezing episodes appear to resolve by the age of 13 [17•]. This finding suggests that, although RSV infections can lead to asthma-like symptoms, they may not actually lead to asthma in the long run.

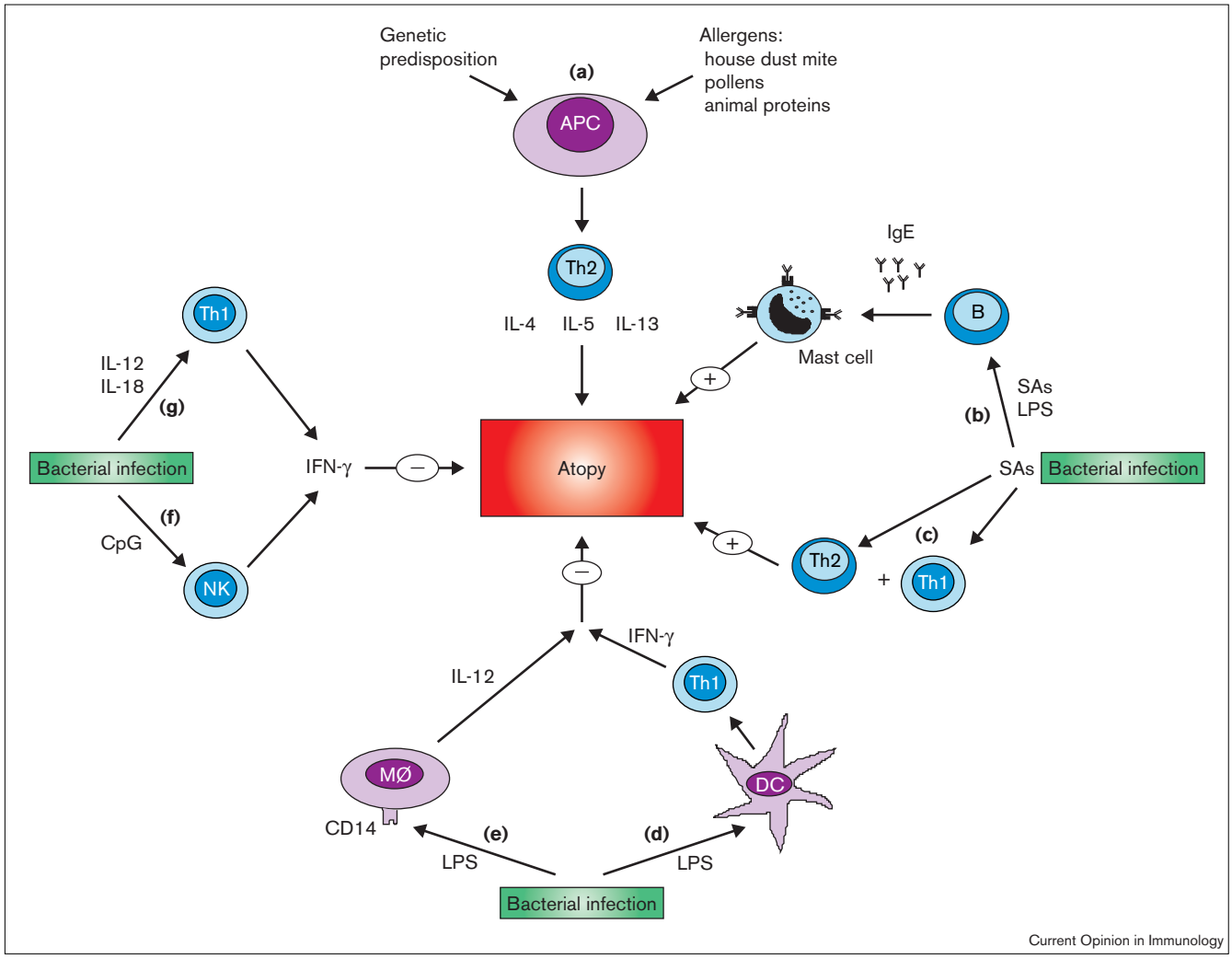
The potential mechanisms by which respiratory viruses may exacerbate allergic symptoms are not precisely understood at present and many hypotheses have been proposed in an attempt to address the observed phenomenon. For example, it is well established that the presence of IL-4 during T cell activation leads to the generation of Th2-type $CD4^+$ and $CD8^+$ cells. It is conceivable that the IL-4 produced during the allergic response may switch the normally predominantly Th1-biased T cell response against the virus towards a Th2-biased response. Virus-specific $CD4^+$ and $CD8^+$ cells secreting IL-4 and IL-5 may then exacerbate asthma by recruiting more eosinophils into the lung and/or inducing the production of virus-specific IgE antibodies, resulting in mast cell degranulation.

It has previously been reported that allergen-mediated sensitization leads to a switch of $CD8^+$ T cells from a Th1 to a Th2 type, leading to airway eosinophilia [18]. This finding was confirmed by a recent report from Adamko *et al.* [19••] demonstrating that parainfluenza virus infection of OVA-sensitized guinea pigs induced IL-4 and IL-5 production. The authors also proposed a model of how eosinophils could be responsible for viral exacerbation of airway hyper-responsiveness, by showing direct interaction of eosinophil-granule-derived major basic protein (MBP) with prejunctional M2 muscarinic receptors expressed on airway parasympathetic nerves. These receptors function by binding newly released acetylcholine to suppress further release of this neurotransmitter as a part of a negative feedback loop. The virus-induced production of IL-5 appeared to evoke the recruitment of eosinophils to the airways of OVA-sensitized animals in intimate association with nerve endings (not seen in nonsensitized mice), where they presumably degranulate (Figure 1d). Eosinophil-derived MPB apparently downregulated M2 receptor function, since the intraperitoneal administration of an anti-MBP antibody partially reversed vagally induced bronchoconstriction in virus-infected, OVA-sensitized animals [19••]. In effect, airway nerves continue to be activated in the presence of degranulating eosinophils, leading to enhanced airway responsiveness.

Earlier studies have already indicated a role for eosinophils and their granule products in airway hyper-responsiveness by blockade of the M2 receptor (reviewed in [20]). Taken together, evidence suggests that eosinophils appear to be important for establishing virally induced airway hyper-responsiveness, providing a potentially very concise model of bronchial hyper-reactivity in virally infected asthmatics.

It is self-evident that viral infections that induce Th2 responses should lead to the exacerbation of atopic disorders. However, wheezing is often associated with viruses that do not induce Th2 responses. One possibility is that the inflammatory Th1 response in the lung that occurs through the induction of proinflammatory cytokines and chemokines may simply exacerbate the allergic disorder by increasing an influx of inflammatory cells into the airways. In support of this view are the findings that children with virus-induced asthma were found to exhibit an increase in IFN-γ in respiratory secretions [21] and that RV induces an IL-1-β-dependent increase in airway smooth-muscle contraction *in vitro* [22] (Figure 1b). Interestingly, IFN-γ has

Figure 2



A model of how bacterial infections may influence the development of atopic disorders. **(a)** Genetic factors and environmental allergens determine whether allergen-specific Th2 cells are generated, leading to the development of atopy. Bacterial infection may have a variety of effects and, for simplicity, these are shown emanating from the right, lower centre and left of the figure. **(b)** Bacterial infection may lead to the production of SAs and LPS. SAs can act as conventional allergens, leading to the exacerbation of the allergic phenotype by SA-specific IgE mediating mast cell degranulation. LPS directly augments already established IgE responses, thereby exacerbating allergic disease. **(c)** SAs can also directly interact with the TCR, triggering profound T cell activation. The activation of Th2 cells directly increases allergic responses whereas the stimulation of Th1 cells contributes to chronic, severe atopic disease. **(d)** LPS induces the development of DCs that preferentially induce the development of Th1 cells and lead to the suppression of atopic disease. **(e)** Macrophages (MØs) that are activated by LPS (via CD14) secrete IL-12, possibly contributing to the inhibition of allergen-specific Th2 cell development. **(f)** Bacterial DNA with CpG-containing oligonucleotides activates NK cells, resulting in the production of IFN-γ and leading to a suppression of allergic Th2 responses. **(g)** Bacterial infections that induce strong Th1 responses directly inhibit the development of allergen-specific Th2 cells through the production of IFN-γ, IL-12 and IL-18 at the site of naive T cell priming.

been shown to increase the secretion of the chemokine, RANTES, from eosinophils [23•] and, in combination with RSV, from eosinophils and bronchial epithelial cells [24]. Since RANTES is associated with increased Th2 cell influx and eosinophilia [25], it is possible that viral infections that induce Th1 responses can exacerbate asthma locally by indirectly increasing the amounts of RANTES produced in the lung (Figure 1e). The observation that RANTES levels were elevated in respiratory secretions of children during episodes of virus-induced asthma (and not during the asymptomatic period) supports this view [26].

However, IFN-γ may not always be a necessary component for virus-induced chemokine release by eosinophils, since RVs have been shown to bind to eosinophils via ICAM-1, possibly directly activating the eosinophils [27]. A further cytokine that may be important in mediating virus-induced exacerbation of asthma is IL-8, a powerful proinflammatory chemokine that is chemotactic for neutrophils. It was reported that both RV [28] and RSV [29] could induce the production of IL-8 by lower-airway epithelial cells *in vitro*. Patients infected with RSV also showed an increase in IL-8 in lower-airway secretions [29].

This implies that both RV and RSV infections could exacerbate asthma through the recruitment of neutrophils into the site of allergic inflammation (Figure 1f).

Taken together, it is clear that almost all respiratory viral infections could potentially exacerbate asthma both in experimental animal models and humans. However, none of these viruses appears to induce atopic disease. In addition, there does not seem to be a common mechanism responsible for enhancement of allergic symptoms. Rather, it seems that many different mechanisms could operate at the same time and potentiate one another. These include an indirect effect on the T cell phenotype — for example by immune deviation causing a switch from Th1 to Th2 responses in the lung — or a direct effect by the virus, inducing a Th2 response where none existed before. Importantly, a Th1 response induced by respiratory viruses may also facilitate Th2-mediated inflammation by increasing the production of proallergic chemokines, such as RANTES, by eosinophils or epithelial cells. Lastly, viral infections may cause wheezing without an underlying allergic phenotype by directly causing M2 muscarinic dysfunction on vagal nerve endings, leading to bronchoconstriction. Figure 1 shows a model of how viral infections may influence allergic disorders.

The influence of bacterial infections and antigens on the development and exacerbation of atopic disorders

Do bacterial infections inhibit the development of atopic disorders?

Similar to viral infections, most bacterial infections — in particular obligate intracellular pathogens — induce profound Th1 responses, with high levels of IFN-γ secreted predominantly by $CD4^+$ T cells and usually not by $CD8^+$ T cells. However, in contrast to viral infections, there are many studies suggesting that bacterial infections and/or bacterial products can inhibit the development of allergic disorders. For example, Shirakawa *et al.* [30] reported that a positive tuberculin test result, suggestive of past infection with *Mycobacterium tuberculosis*, was inversely related to the subsequent development of atopy and asthma.

An alternative explanation is that atopic children (Th2 responders) have difficulties in mounting an appropriate and sufficient Th1 response following vaccination. This would explain the lower frequency of positive tuberculin responses in atopic children compared with non-atopics. Recently it was reported that BCG vaccination given early in infancy may prevent the development of atopy in African children [31]. However, several authors showed that vaccination with BCG per se does not prevent the development of allergy and asthma [32,33]. A negative tuberculin response in vaccinated infants is therefore suggestive of a failure to develop appropriate Th1 immunity. In line with this explanation is the observation by Prescott *et al.* [34], that total IgE levels correlate inversely with positive skin-test responses to tetanus and diphtheria toxin in vaccinated infants, again suggesting that a high Th2 propensity prevents appropriate Th1 immunity.

Recently, however, Von Mutius *et al.* [35] reported a significant inverse correlation between the prevalence of asthma and reported rates of tuberculosis. The observation that an infection in the lung with live BCG prevented allergen-induced airway eosinophilia and the development of airway hyper-reactivity in mice [36,37] further supports the idea that mycobacterial infections prevent the development of atopy. How can mycobacterial infections mediate this effect? A recent report showed that — in wild-type mice but not IFN-γ-receptor-deficient mice — airway eosinophilia induced by allergen-specific Th2 clones could be suppressed by allergen-specific Th1 clones, which were simultaneously transferred [38••]. This suggests that IFN-γ secreted by Th1 cells leads to a reduction in airway eosinophilia. This could also be the case during mycobacterial infections, which are known to induce a profound Th1-type immunity. However, the exact mechanism of how IFN-γ mediates this effect is not clear.

Interestingly, it appears that bacteria do not have to be alive to prevent allergic responses, since killed *Listeria monocytogenes*, *M. vaccae* or *Lactobacillus plantarum* could also suppress allergic responses in mice [39–41]. Furthermore, oligonucleotide motifs that contain CpG (these are found in the DNA of many different types of bacteria but not in eukaryotic organisms) have been found to be potent stimulators of IL-12 and IFN-γ production, perhaps leading to a strong inhibition of allergic airway inflammation (reviewed in [42]). This suggests that the exposure to bacterial DNA in general could lead to enhanced suppression of atopy. However, it is not clear whether DNA containing CpG-oligonucleotides is released in sufficiently stimulatory amounts during infection to have this effect.

Taken together, there is strong evidence suggesting that bacterial infections can prevent the development of allergy in animals. The exact mechanism(s) of how this is achieved is still not understood, except that it may involve IL-12 and/or IFN-γ. In humans, it is unclear if, and which, bacterial infections could lead to decreased atopy. However, the finding of Wickens *et al.* [43], that the use of antibiotics during infancy correlates with an increased risk of developing asthma, suggests that bacterial infections early in life may help to inhibit the development of asthma. However, due to the correlative nature of this study, more human studies are needed before reaching the conclusion that decreasing antibiotic treatment leads to a reduced risk for atopy later in life. Figure 2 shows a model of how bacterial infections might influence the development of allergic disorders.

Exposure to lipopolysaccharide and the development of atopy

Most recently, several authors reported that growing up on farms and being exposed to livestock confers significant protection against the development of atopy [44,45]. A

potential candidate, among others, in mediating this protection is the exposure to bacterial endotoxins, such as lipopolysaccharide (LPS), on farms. Supporting this hypothesis is the finding that there is an inverse correlation between concentrations of house-dust endotoxin and allergen sensitization, since skin-test-negative children were exposed to significantly more house-dust endotoxin [46•].

One mechanism by which LPS may trigger Th1-type immunity is via binding to the LPS receptor, CD14, which is expressed by APCs, particularly monocytes. Binding of LPS to CD14 results in marked stimulation of IL-12 production, which seems to be one of the most important inducers of Th1 responses (Figure 2e). It is of interest that a polymorphism in the 5′-flanking region of the CD14 gene has been associated with the increased intensity of atopy [47•]. More recently, a study showed a correlation between concentrations of house-dust endotoxin and the frequency of IFN-γ-secreting T cells in the blood [46•].

These findings indicate that exposure to LPS may be of great biological relevance in generating appropriate Th1 immunity to environmental allergens. Furthermore, Stumbles *et al.* [48] reported that the resident dendritic cell (DC) population of the respiratory tract of rats preferentially induces the development of Th2 cells [48]. In the presence of GM-CSF or TNF-α, the DCs induced a response that was skewed towards the development of a Th1 response. Since LPS leads to the secretion of TNF-α by macrophages, it may be possible that LPS exposure leads to increased Th1 responses against inhaled allergens by altering the stimulatory quality of the mucosal DCs from Th2-type towards Th1-type (Figure 2d). However, exposure to LPS was shown to have bi-directional effects in animal models: LPS given after allergen-sensitization increased IgE production and airway inflammation [49–51]; in contrast, exposure to LPS after airway allergen-challenge abolished airway inflammation and bronchoconstriction [51,52].

Taken together, there is circumstantial evidence suggesting a role for LPS in the development of allergic disorders. However, the underlying molecular and cellular mechanisms are still unknown. The source and route of exposure to LPS may also be important, since LPS is produced by several bacterial pathogens (e.g. *Haemophilus* and *Salmonella*) and commensals colonizing the gut (e.g. *Escherichia coli*). Interestingly, Björksten *et al.* [53] found that the colonization of the gastrointestinal tract from new-born babies who had lactobacillus and eubacteria (compared with those who had *Clostridium difficile*) correlated with a decrease in atopic disorders later in life. This suggests that commensal gut bacteria may play an important, as-yet unrecognized role in predisposing children towards the atopic phenotype.

Influence of superantigens derived from *Staphylococcus aureus* on the development of atopy

The prominent role of skin colonization with *S. aureus* as a factor contributing to the exacerbation of atopic dermatitis has been well established. Unlike conventional antigens, toxins from *S. aureus* stimulate T cells in their native state via direct binding and stimulation of TCR Vβ elements. Depending on the TCR repertoire, up to 25% of T cells were shown to be responsive to such superantigens (SAs), leading to vigorous T cell activation and cytokine release. Moreover, *S.-aureus*-derived toxins can function not only as SAs but also as conventional allergens (Figure 2b). Several studies promote the concept that SAs have disease-promoting effects. Specific IgE antibodies directed against staphylococcal enterotoxin A or B were detectable in a subgroup of atopic dermatitis patients. The presence of these SA-specific IgE antibodies strongly correlates with disease severity and IgE levels [54]. Furthermore, a preferential accumulation of SA-responsive T cells was observed in patients with intense skin inflammation [55]. Additional evidence for a disease-modulating effect of SAs has been provided by a study performed by Strickland *et al.* [56]. They showed that, *in vitro*, SAs have the capacity to activate and expand T cells expressing specific TCR Vβ gene segments and also to increase their skin-homing capacity via upregulation of the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA) *in vitro* [56]. Moreover, SA-induced T cell activation also seems to be involved in dermatitis. Skov *et al.* [57•] showed that the application of staphylococcal enterotoxin B on normal and atopic skin induced an influx of T cells into the skin, leading to the induction of dermatitis.

Other pathogens possibly influencing the development of atopic disorders

Other types of pathogens possibly having an effect on the development of allergic disorders include infections caused by fungi or parasites. Although it is well established that humans directly develop allergies against fungal antigens (for example, spores from *Aspergillus* species) or after infection with cryptococci, there is little evidence suggesting that fungal diseases have any major influence on the development of atopy. However, it was reported that the colonization with *Candida albicans* is associated with severe eczema [58].

A further group of pathogens that could have an impact on allergic responses in humans are protozoans. Although these pathogens induce profound immune responses (in particular, plasmodia, leishmania and trypanosomes), no clear data are available on the role of protozoans in the etiology of atopy.

In contrast to fungal or protozoan infections, there is some evidence suggesting that helminthic infections may influence the development of atopic disorders. In contrast to most other type of infections, helminths almost exclusively induce Th2-type responses. Therefore, worm infections would be expected to promote atopy through the induction of IL-4 expression, leading to increased development of allergen-specific Th2 cells. Furthermore, the increase in total eosinophil numbers and induction of mastocytosis

observed after worm infections may directly increase allergic-type inflammation. The mechanical irritation at sites of allergic inflammation during worm migration may also increase the atopic phenotype by generally increasing inflammatory responses at these sites.

Supporting this view are the findings that infections with *Nippostrongylus brasiliensis* [59] and *Brugia malayi* [60] induce airway hyper-responsiveness in mice. Furthermore, anti-helminthic treatment of individuals living in regions with a high prevalence of worm infections also resulted in the improvement of asthma [61]. Allergic manifestations also seem to occur more often in children who are seropositive for *Toxocara* or *Ascaris* than in seronegative children [62,63]. These reports suggest that helminth infections generally lead to the exacerbation of atopic disorders and it would be expected that countries with a high prevalence of helmith infections would also have a high atopy rate. Interestingly, the opposite is true. The basis for this observation is not clear but it has been suggested that, although helminths may actually increase Th2 responses towards allergens, they may also inhibit atopic effector functions by inducing the production of polyclonal IgE. High amounts of IgE could saturate the Fcε 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. However, it has also been suggested that the development of Th2 responses directed against environmental antigens may simply reflect a default mechanism in the absence of infection because a highly efficient and conserved response is no longer being used by the immune system [64•].

Conclusions

It is clear that infections can, under certain conditions, influence the onset, maintenance and exacerbation of allergic diseases both in animal models and humans. However, there is no one, clear-cut effect. Rather, several mechanistic pathways may work independently of each other or have additive and/or synergistic effects that result in the inhibition or exacerbation of atopy, depending on the infectious agent and the time-point of the infection. If the infection occurs before or during allergen sensitization, it is likely that this will lead to the reduction of the emerging atopic phenotype. On the other hand, if the infection takes place after the development of an established allergic Th2 response, the allergy will be exacerbated. This is probably generally true for both viral and bacterial infections. However, there seems to be an association between viral/bacterial infections and the exacerbation/reduction of atopy, respectively. The reason for this observation is not clear but may simply be due to the qualitative differences between the immune responses against viruses and bacteria.

A further factor that is believed to be important in the etiology and evolution of atopic disorders is infection with helminths. Although it is plausible that the Th2 responses initiated against helminths can exacerbate atopy, or alternatively suppress allergic effector functions, there is no clear evidence suggesting a positive or negative role of helminth infections on the development of allergic diseases. In this context it is important to point out that the interpretation of epidemiological studies is often very difficult because resistance or susceptibility towards infections or atopy may either be mutually inclusive or exclusive. However, the importance of such studies cannot be overemphasized since they may lead to an explanation of why atopic disorders are currently increasing at such an alarming rate. Furthermore, more knowledge about the underlying mechanisms responsible for infection-induced inhibition or exacerbation of atopic disorders may lead to novel therapeutic and prophylactic intervention strategies that help to control allergic diseases in the future.

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