

REVIEW

Role of dendritic cells: a step forward for the hygiene hypothesis

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The hygiene hypothesis was proposed more than two decades ago, but its mechanism remains unclear. This review focuses on recent advances in the field, especially on the role played by dendritic cells (DCs) and their modulating effects on various infections and allergic diseases, including allergic asthma. DCs isolated from mice long after the resolution of an infection were reported to have a significant modulating effect on allergen-specific Th2 responses in both *in vitro* and *in vivo* systems. These DCs showed DC1-like and/or tolerogenic DC capacity, which allowed for the inhibition of allergic responses by immune deviation (enhancing Th1 response) and immune regulation (through regulatory T-cell and Th2 hyporesponsiveness) mechanisms. These findings represented a significant advance in the elucidation of the mechanisms underlying the hygiene hypothesis. Further investigation on the mechanisms by which DCs are 'educated' by infectious agents and the influence of the type, time, and extent of infections on this 'education' process will help us understand immune regulation in disease settings and in the rational design of preventive/therapeutic approaches to allergy/asthma and infections.

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INTRODUCTION

For decades, an inverse relationship between infections and allergic diseases has been observed in most developed countries. The 'hygiene hypothesis' suggests that exposure to microbial infections or microbial products may inhibit the development or pathogenesis of allergic responses, including asthma.^{1–5} Many epidemiological observations related to various infections support this provocative hypothesis.^{6–14} In particular, a series of studies have described children who had close contact with farm animals and exhibited significantly lower levels of allergy and asthma later in life. In addition, previous research has found that some bacteria isolated from farm cowsheds have allergy-preventive properties.^{14–17} These large scale, relatively well-controlled series of epidemiological studies have provided strong evidence for the imprinting effect of infection on the immune system and on the prevention of allergic diseases. Moreover, a recent, thoroughly performed systematic review and meta-analysis of 23 published papers (up to June 2008) examined the relationship between early life *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG) exposure, as demonstrated by history of BCG vaccination, tuberculin response and scar diameter, and asthma; the review included 10 cohort, 5 case-control and 8 cross-sectional studies, and it found a clear inhibitory effect of BCG vaccination on the development of asthma.¹⁸

In addition to epidemiological observations, experimental studies have also provided support for the hygiene hypothesis.^{19–30} For example, BCG infection prevented the development of asthma-like

reactions in a murine asthma model.^{19,20} Some studies showed that systemic or mucosal administration of killed bacteria, introduction of bacterial CpG, and intramuscular infection with adenovirus also inhibit allergic reactions.^{21–26} We have shown that the *Chlamydia trachomatis* mouse pneumonitis strain, more recently called *C. muridarum*, and BCG infections have a significant imprinting effect on newborn or young adult C57BL/6 and Balb/c mice; the imprinting inhibited allergy/asthma induced by natural or model allergens later in life.^{31–38} In particular, *C. muridarum* infection had a strong imprinting effect on the inhibition of allergy, even after the infection had long been cleared.^{35–38} Moreover, recent studies demonstrated an inhibitory effect of parasitic infections on allergy/asthma.^{27–30}

However, this hypothesis currently faces numerous challenges,^{39–45} because some epidemiological studies have been performed on populations with different genetic backgrounds, culture, economic development stage, health care system and geographical location, and they have shown either no relationship between infection and allergy, especially asthma, or an increased risk of allergic asthma in association with infection.^{40–46} In experimental models, some infections, such as acute infections, exacerbated already established allergy/asthma or enhanced allergic reactions when the allergen and infectious agents were co-administered.³⁹ In general, the imprinting effect of previous bacterial infections on the inhibition of allergy and asthma development or pathogenesis is more commonly observed than the effect of recent or concurrent infections.

IMMUNOLOGICAL BASIS FOR INFECTION-MEDIATED INHIBITION OF ALLERGY

The underlying mechanisms for the inverse relationship between exposure to microbes or microbial substance and development of allergy are still ill defined. However, from an immunologic point of view, the involvement of innate and adaptive immune responses, especially the interaction between these two types of immune responses, is likely to occur. In particular, microbial infections may modulate Th2-like allergic responses by promoting immune deviation (toward a Th1 response) and/or enhancing immune regulation, depending on the nature of the infectious agents, the time and duration from exposure to infection, the extent and stages of the infection, and the genetic background of the host.

Immune deviation

Since allergy is a typical Th2-type disease, many bacterial infections induce a Th1 response, so earlier studies mainly focused on immune deviation.⁴⁷ The shift from a Th1 to Th2 response was hypothesized to be due to a reduction in infection load and was discussed as the reason for the increased prevalence of allergic diseases. The groundbreaking study by Shirakawa *et al.* provided evidence to support that hypothesis by showing an inverse correlation between the intensity of tuberculin reaction and the likelihood of developing an atopic disease in later life.⁶ Many subsequent studies also showed supportive data for the importance of immune deviation in the prevention of allergy.^{19,20,24–26}

Immune regulation

Although the relationship between the Th1-promoting effects of infections and the consequent inhibition of allergy provides an explanation for the hygiene hypothesis, the mechanism has been challenged because some Th1-type autoimmune diseases have also increased over the past decades. Moreover, some pro-Th2 parasitic infections were found to also inhibit allergic diseases. Therefore, a lack of, or diminished, Th1-type promoting effect induced by an infection is unlikely to be the predominant mechanism for the observed increase of allergic diseases in developed countries. In addition, although many epidemiological and experimental studies have shown that pro-Th1 infections/vaccinations, such as BCG, have an inhibitory effect on the development of allergic responses, not all studies showed the same effect. Rather, the lack of a regulatory mechanism for the development of allergic responses may be involved and may even be more relevant in certain circumstances.^{48–51} The regulatory mechanism likely involves: (i) the induction of various types of regulatory T cells (Tregs), which produce/express IL-10 and/or transforming growth factor (TGF)- β and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4); (ii) the unresponsiveness of effector T cells; and (iii) the apoptosis of allergen-specific Th2 cells.

Tregs play an important role in regulating allergic reactions.⁵² The two major groups of Tregs include naturally occurring CD4⁺CD25⁺ Tregs (nTregs), which mainly develop in the thymus,^{53,54} and inducible Tregs, which develop in the periphery from conventional CD4⁺ T cells. Foxp3 is a typical marker initially identified in nTregs, but it is also expressed by some inducible Tregs.^{55,56} The relationship between the Foxp3⁺ nTregs and Foxp3⁺ inducible Tregs remains unclear. The inducible Tregs may include IL-10-producing regulatory type 1 (Tr1) cells, TGF- β -producing Th3 cells and converted Foxp3⁺ Tregs. Th1-like Tregs have also been reported to produce both IL-10 and interferon (IFN)- γ .⁵⁷ Different types of Tregs may inhibit allergic reactions through antigen-specific and/or antigen-non-specific mechanisms. The role of Tregs in infection-mediated inhibition of allergy has been

documented in studies on parasitic infections, especially helminth infections.^{58–63} The involvement of Tregs in bacterial infection-mediated modulation of allergy/asthma has been reported, but is much less studied.^{64–66} In particular, subcutaneous treatment with heat-killed *Mycobacterium vaccae* was reported to induce CD4⁺CD45RB^{low} T cells, which inhibited asthma through IL-10 and TGF- β production.^{65,66}

Therefore, microbial infections may modulate Th2-like allergic responses by promoting immune deviation (toward a Th1 response) and/or enhancing immune regulation depending on the nature of the infectious agents, the extent/stages of the infections and the genetic background of the hosts.

CONTRIBUTION OF DENDRITIC CELLS (DCS) IN INFECTION-MEDIATED INHIBITION OF ALLERGY/ASTHMA

Although changes in immune deviation and immune regulation have been documented in numerous studies, until recently, the mechanisms for these changes remained largely unknown. In particular, how the immune deviation happened and how T-cell tolerance/Tregs were generated, as well as their roles in infection-mediated inhibition of allergy/asthma, were unknown. Recently, work from our group and others demonstrated that the modulating effect of infections on the function of DCs is likely the basis of infection-mediated inhibition of allergy and asthma. As a critical link in innate and adaptive immune responses, DCs provide a platform for microbial products to modulate Th2 cell responses.

T-cell responses and DC function

DCs are particularly important antigen-presenting cells because they induce primary T-cell responses and modulate T-cell polarization. DCs are heterogeneous in terms of cell lineage, stage of maturation and function. DCs isolated *ex vivo* can be grouped into lymphoid/plasmacytoid and myeloid lineages.⁶⁷ In mice, the lymphoid DCs are CD8 α ⁺, while the myeloid lineages are CD8 α ⁻. In addition to these two conventional DCs, plasmacytoid DCs (pDCs) have also been identified in humans and mice. pDCs are characterized by their high expression of B220 and mouse pDC antigen, and mouse pDCs have a high level of IFN- α production.⁶⁸ The relationship between DC phenotype/lineage and the role of DCs in immune regulation, in both humans and mice, is a controversial issue.^{69–73} In mice, splenic CD8 α ⁺ lymphoid DCs (DC1) were initially found to primarily promote a Th1 response, whereas the CD8 α ⁻ myeloid DCs (DC2) were found to promote Th2 differentiation.^{74,75} However, later studies challenged this one cell type-one type of response concept by showing that DCs with distinct functional properties may emerge from the same precursors,^{76,77} and that CD8 α ⁺ DCs could also play a regulatory role. Therefore, DCs are believed to be largely plastic in function, and the expression of costimulatory markers and cytokines/molecules is likely to be more important for characterizing functional DC subsets.^{78–86}

Tolerogenic/regulatory DCs (DCregs), which may cause T-cell tolerance by different mechanisms, including T-cell depletion (apoptosis), T-cell hyporesponsiveness (anergy) and Treg induction, may be involved in the inhibition of allergic Th2 responses (Figure 1). Some CD8 α ⁺ DCs express higher levels of Fas ligand (FasL) and are able to cause T-cell apoptosis.^{87,88} The apoptosis is mediated by the interaction of FasL on CD8 α ⁺ DCs with Fas on activated T cells.⁸⁹ DCs treated with IL-10^{90–92} may induce T-cell anergy. Immature DCs, or DCs with altered maturation status, may induce Treg development. Some specialized DCs can induce Tregs even in their fully mature state. Levings *et al.* proposed a model of two-step differentiation in Tregs:⁹¹

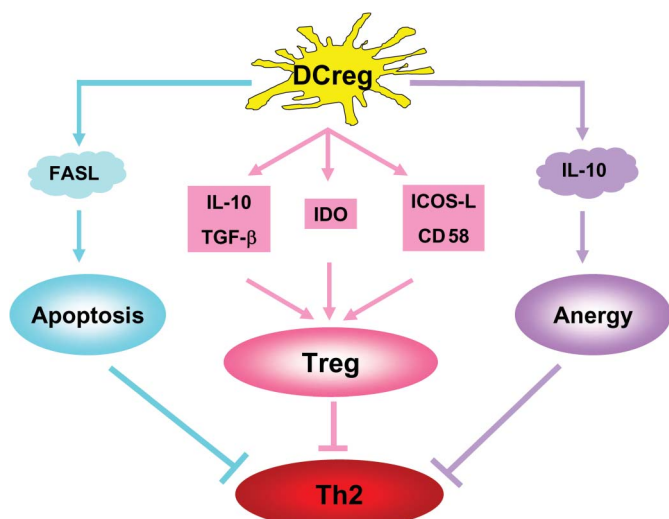


Figure 1 The mechanisms by which tolerogenic DCs/DCregs inhibit allergic Th2 responses. DCregs induced by infection or exposure to bacterial components can inhibit allergic Th2 responses through three mechanisms: (i) DCregs can express FasL, which leads to Th2 cell apoptosis through FasL–Fas interaction (blue line); (ii) DCregs can induce allergen-specific and allergen-non-specific Tregs through the production of immunoregulatory cytokines such as IL-10 and TGF- β , enzymes such as IDO, and costimulatory surface markers (red line); and (iii) DCregs may induce Th2 cell anergy through the production of IL-10 and other cytokines. \rightarrow : promoting effect; \vdash : inhibitory effect. DCreg, regulatory dendritic cell; FasL, Fas ligand; ICOS-L, inducible costimulatory ligand; IDO, indoleamine 2,3-dioxygenase; TGF, transforming growth factor; Treg, regulatory T cell.

in the first step, naive T cells encounter antigen presented by DCs in the presence of IL-10 and possibly TGF- β , and they become hyporesponsive to the antigen through a cell–cell contact dependent process; in the second step, following repeated antigen exposure, these T cells gain their ability to produce IL-10 and TGF- β , and they mediate suppression through a cytokine-dependent, cell–cell contact-independent mechanism. The fully differentiated Tregs are more potent in their suppressive activity than anergic T cells.

The molecular basis for the capacity of tolerogenic DCs to induce Tregs may be related to their cytokine production and the expression of intracellular enzymes and surface molecules (Figure 1). The production of IL-10, TGF- β and IFN- α by DCs, either as individual cytokines or in combination, is particularly important for the induction of Tregs.^{93–100} Interestingly, an intracellular enzyme indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan and triggers cellular stress responses, also participates in the immune regulation of chronic infections.⁹³ An IDO-expressing subpopulation of pDCs showed potent regulatory properties by inducing Tregs.⁹⁴ In terms of surface markers, certain molecules such as inducible costimulatory ligand (ICOS-L), CD58, OX-2 and programmed death-1 ligands can promote the development of Tregs.^{93,101–103} pDCs appear to be particularly relevant for tolerogenic DCs, which express high levels of ICOS-L, IDO, IFN- α and Toll-like receptor (TLR)-9.

Critical role of DCs in infection-mediated inhibition of allergy

The critical importance of DCs in infection-mediated inhibition of allergy has been shown in recent reports.^{33–38,63} These studies suggested that different infections may ‘educate’ DCs to become DC1-like cells, which promote a Th1 response and subsequently inhibit allergic Th2 responses (immune deviation), and/or these DC1-like cells become tolerogenic DCs/DCregs, which induce Tregs or have a

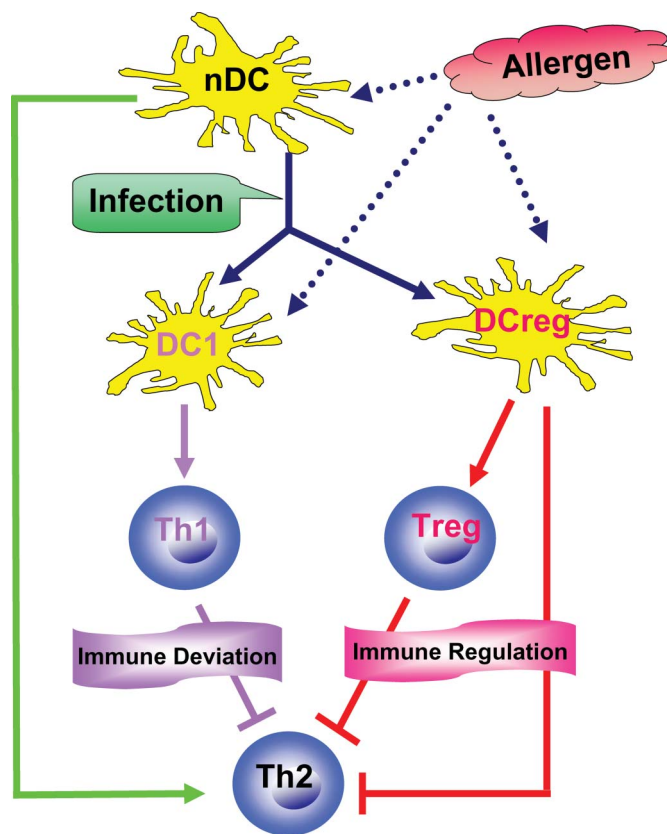


Figure 2 The central role of DCs in infection-mediated inhibition of allergic responses. Allergens presented by nDCs induce allergic Th2 responses (green line). DCs educated by *in vivo* infection may become DC1-like cells (DC1) and/or tolerogenic DCs/DCregs. Allergens presented by DC1-like cells can activate Th1 cells, which inhibit allergic Th2 responses (immune deviation), whereas those presented by DCregs can induce Tregs or have a direct suppressing effect, thus inhibiting allergic Th2 responses (immune regulation). \rightarrow : promoting effect; \vdash : inhibitory effect. DC, dendritic cell; DCreg, regulatory dendritic cell; nDC, normal dendritic cell; Treg, regulatory T cell.

direct inhibitory effect on allergic Th2 cells (immune regulation) (Figure 2). We first reported that DCs freshly isolated from *C. muridarum*-infected mice, but not DCs from naive mice, could inhibit the systemic and cutaneous eosinophilia inflammation normally induced by exposure to an allergen upon adoptive transfer.³³ The reduction of eosinophilia inflammation was associated with a decrease in IL-5 receptor expression on bone marrow cells and a decrease in the production of IL-5 and IL-13 by T lymphocytes. Coculture of DCs with naive CD4⁺ cells from ovalbumin (OVA) peptide TCR-transgenic mice (DO11.10) showed that DCs from infected mice directed a Th1-dominant response, while DCs from naive mice directed a Th2-dominant, allergen-specific CD4⁺ T-cell response. Upon analysis, the DCs from infected mice were found to express significantly higher levels of TLR-9 and IL-12 compared with DCs from naive mice. More recently, we found that adoptively transferred DCs from BCG-infected mice, but not from naive mice, significantly inhibited established allergic airway eosinophilia and mucus overproduction.³⁸ The inhibitory effect was correlated with a significant increase in Th1-related cytokines (IFN- γ and IL-12) and with a significant decrease in allergen-driven Th2 cytokines (IL-4, -5, -9 and -13). The DCs from BCG-infected mice produced significantly higher levels of IL-12 and expressed higher levels of TLRs than DCs from naive mice. The

blockade of IL-12 dramatically reduced the Th1-enhancing effect of the adoptively transferred DCs, and this reduction was associated with a reversal of the inhibitory effect on allergic airway inflammation and Th2 cytokine responses. Therefore, DCs from mice infected with bacteria can modulate allergic responses through immune deviation.

In addition to the effect on immune deviation, DCs from infected individuals can play a role as tolerogenic DCs/DCregs that induce Tregs or directly inhibit allergic responses.^{34,36,38,57,63,64,66,104} We recently showed that the adoptive transfer of DCs from *Schistosoma japonicum*-infected mice dramatically decreased airway allergic inflammation and was associated with a significant decrease in IL-4/IL-5 production and an increase in IL-10 production.⁶³ The DCs' modulating effect on allergy was related to enhanced CD4⁺CD25⁺Foxp3⁺ Treg responses (Liu Z, Liu P, Yang X, unpubl. data). In addition, bacterial infections can also induce tolerogenic DCs, which inhibit allergic responses. Bacterial products, such as filamentous hemagglutinin expressed by *Bordetella pertussis*, have been found to enhance IL-10 production by DCs and promote Tr1 cells.⁶⁴ Tr1 clones may express T1/ST2 and CC chemokine receptor 5 and secrete high levels of IL-10, but not IL-4 or IFN- γ . In addition, *M. vaccae* was reported to induce a population of IL-10- and TGF- β -producing pulmonary DCs, which may either directly inhibit asthma or indirectly inhibit asthma through the generation of IL-10-producing Tr1 cells.⁶⁶ We found that DCs isolated from *C. muridarum*-infected mice during later stages of infection or after the resolution of the infection produced significantly higher levels of IL-10 and IL-12 than those from naive mice.^{34,36,38} Adoptive transfer of the DCs from the previously infected mice inhibited allergen-driven Th2 cytokine responses. Coculture of DCs from *C. muridarum*-infected mice with CD4⁺ T cells from OVA peptide TCR-transgenic (DO11.10) mice showed reduced Th2-like cytokine responses. Neutralization of either IL-10 or IL-12 in the coculture of DCs and T cells and in adoptive transfer experiments significantly reduced the inhibitory effect on allergen-driven Th2 responses. Moreover, we found that DCs from *Chlamydia*-infected mice expressed higher levels of ICOS-L,³⁴ and we found that ICOS-L expression could potentiate the modulating effect by synergizing with the IL-10 produced by these DCs.³⁴ In our study on the adoptive transfer of DCs from BCG-infected mice,³⁸ we found that these DCs showed increased expression of CD8 α , costimulatory markers and TLRs, and increased production of IL-10 and IL-12. *In vivo* neutralization of either IL-10 or IL-12 significantly reversed the inhibitory effect of these DCs on established allergic airway inflammation and Th2 cytokine responses.³⁸ These results suggested that DCs from bacteria-infected mice might contain IL-10-producing tolerogenic DCs in addition to the IL-12-producing DC1-like cells mentioned above.

The imprinting effect of early life exposure to bacterial products on the inhibition of allergy and its relationship with DC function has also been explored.³⁶ Neonatal exposure to killed bacteria has been reported to alter the surface marker, TLR expression and cytokine production by DCs in adulthood. More importantly, DCs from adult mice treated neonatally with killed bacteria induced significantly lower antigen-specific Th2 responses than DCs from sham-treated mice in experiments with the coculture of DCs and T cells and in adoptive transfer experiments. Interestingly, depletion of T cells *in vivo* largely abolished the phenotypic and functional alterations caused by bacterial exposure, suggesting that the T cells are involved in maintaining the tolerogenic function of DCs. These data demonstrated a central role for DCs in linking early-life exposure to microbial products and the balanced development of immune regulatory functions to allergic

reactions and in the involvement of T cells in the imprinting of DCreg function.

An interesting study using *Listeria monocytogenes* investigated the relationship between DC subsets and the induction of Tregs.⁵⁷ Specifically, co-injection of heat-killed *L. monocytogenes*, OVA-pulsed CD8 α ⁺ DCs and OVA-specific naive CD4⁺ T cells from TCR-transgenic DO11.10 mice induced Th1-like Tregs. The CD8 α ⁺ DC subset produced both IL-10 and IL-12, and the induced Th1-like Tregs produced IFN- γ and IL-10 and expressed ICOS, Foxp3 and T-bet. These Th1-like Tregs significantly inhibited allergic reactions.⁵⁷ Consistently, we found that both *Chlamydia* and BCG infections preferentially enhanced CD8 α ⁺ DC expansion.^{38,105} More interestingly, we found that CD8 α ⁺ DCs isolated from *Chlamydia*-infected mice produced significantly higher levels of IL-12 and IL-10.¹⁰⁵ When the inhibition potency on allergic reactions was compared, CD8 α ⁺ DCs were more effective in inhibiting *de novo* and established allergic reactions (Bilenki L, Yang X, unpubl. data). However, it remains unclear whether these DCs belong to one DC subset or several subsets. It would be interesting to know whether the CD8 α ⁺ DC subset from *Chlamydia*-infected mice can induce Th1-like Tregs and whether these potential Tregs play a role in the DC-mediated inhibition of allergen-specific Th2 responses.

Not all studies of DCs modified by bacterial antigens exhibited an inhibition of allergy. Schröder *et al.* reported that the adoptive transfer of DCs isolated from the lungs of *C. pneumoniae*-infected mice, but not those from phosphate-buffered saline-treated mice, induced allergic sensitization.¹⁰⁶ Notably, the DCs were isolated during early stage infection (day 5), and the DCs were incubated with allergen overnight before adoptive transfer. More recently, a study on neonatal infection of mice with *C. muridarum* found that DCs isolated from infected mice induced higher IL-13 production by OVA-specific TCR-transgenic CD4⁺ T cells in a DC and T-cell coculture system, suggesting that IL-13 had a promoting effect on the DCs from infected mice.¹⁰⁷ No adoptive transfer experiments were performed to test the *in vivo* function of the DCs in that study. We also found that, although DCs from adult mice with neonatal exposure to killed bacteria inhibited the development of allergic reactions in recipient mice after adoptive transfer, DCs from young mice with short exposure to the same bacteria failed to inhibit the development of allergic reactions; this failure was associated with the lack of IL-10 production by the latter DCs (Jiao L, Yang X, unpubl. data). In addition, in adult mice we found that the capacity of the DCs from infected mice to produce IL-10 was influenced by the stage of infection; an increase in IL-10 production by DCs was observed only in later stages of infection.^{33,34} Therefore, the conclusion can vary depending on the model system and methodology used. Careful control of the experimental system and objective analysis of the advantages and disadvantages of different experimental systems, is critical for generating meaningful data to explain the mechanisms of the hygiene hypothesis.

CONCLUDING REMARKS

The relationship between infection and allergy is likely influenced by multiple factors, including the type of infections/microbial substances, time and duration of exposure, and genetic factors, among other potential factors. In particular, different infectious organisms, and even various components of the same infectious agent, may have varying influences on allergy. Moreover, the modulating effect of infections on allergy and asthma may be potentiated or diminished by other factors. For example, although the inhibitory effect of BCG vaccination on asthma has been well documented,¹⁸ the prevalence of

asthma has still increased significantly during the past two decades in developing countries, in which most people are vaccinated with BCG after birth.¹⁰ Compared to the relationship of infection with allergy, the relationship of infection with asthma is even more complicated because not all asthma cases are related to allergy and, even for those that are related, numerous processes may contribute to the development and exacerbation of the disease. Therefore, although the hygiene hypothesis is a credible explanation, it is unlikely to be the sole explanation for the observed increase in allergic diseases during the past decades. Therefore, it is not surprising that inconsistent findings are often reported on this topic. This inconsistency emphasizes the critical importance of mechanistic studies on the relationship between infection and allergy/asthma using well-established experimental models, especially those that are well controlled for the type of infection, condition of infection and host genetic background. At the same time, the difference between humans and animals should also be kept in mind when interpreting research data. The recent finding on the critical role of DCs in the infection-mediated inhibition of allergy and asthma represents a significant advance in elucidating the mechanism for the hygiene hypothesis. Moreover, although allergic asthma is mainly a Th2-related disease, recent studies have shown that the Th17 cell, a newly identified effector T cell, may also contribute to allergic inflammation.^{108,109} DCs are important for Th17 cell development, but the role of post-infection DCs in modulating allergic Th17 responses has not been addressed. Further investigation into the mechanisms by which DCs are 'educated' by infection at different stages of host development will enhance the understanding of immune regulation in disease settings and will be useful in the rational design of preventive/therapeutic approaches to allergy/asthma and infections. In particular, the following questions should be addressed:

1. What determines the heterogeneity of DCs (tolerogenic or DC1-like) in different types/conditions of infections, especially parasitic and bacterial infections?
2. How do different types of DCs that are 'educated' by single or combined infections modulate allergic/asthmatic reactions?
3. How do the infection-imprinted DCs maintain their tolerogenic/regulatory functions *in vivo*?

On the other hand, although the hygiene hypothesis is unlikely the sole explanation for the observed increase in allergic diseases, the information generated from the epidemiological, experimental and clinical studies in this field is still very useful for the design of prevention and treatment approaches for allergic diseases. In particular, it is worthwhile to carefully test the protective capacity, safety and mechanisms of the infectious/microbial products that have been found in experimental studies to be protective for allergic diseases. Learning and mimicking the mechanisms by which these protective microbes modulate allergy, including the involvement of DCs in the process, is important. A good example is the testing of probiotics for the prevention of allergy in clinical trials.^{110–112} A double-blind, randomized, placebo-controlled trial in Finland has shown encouraging results that the ingestion of probiotics, in the form of a non-pathogenic microorganism such as *Lactobacillus GG*, by expectant mothers can decrease the incidence of atopic dermatitis.^{110,111} This perinatal protection can last up to 7 years.¹¹¹ Another trial showed improvement of atopic dermatitis in response to treatment with other strains of probiotics.¹¹² The ultimate goal of this field of research is to develop new methods, or improve upon old methods, for the prevention and treatment of allergic diseases. If this goal can be met, then the validity of the hygiene hypothesis becomes less important.

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