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EXPERT REVIEWS

The role of *Helicobacter pylori* infection in the development of allergic asthma

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Asthma is one of the most prevalent chronic diseases in developed countries, with steady increases in asthma prevalence evident, particularly in the last few decades. As genetic factors are unlikely to contribute to the rise in asthma prevalence, changes in lifestyle and exposure to environmental stimuli have been proposed to account for this trend. The 'disappearing microbiota' hypothesis postulates that major shifts in the human microbiome, resulting from dramatic lifestyle changes, account for the increase in asthma prevalence. In this context, persistent gastric colonization with the human-specific pathogen *Helicobacter pylori* has been negatively associated with the occurrence of asthma in epidemiological studies. In addition, experimental models of allergic airway disease revealed a direct link between infection with *H. pylori* and suppression of allergic airway disease through the induction of regulatory T cells. These and other new insights hold the promise of opening up new avenues toward the development of innovative, new strategies directed at asthma treatment and prevention.

KEYWORDS: asthma • dendritic cells • *Helicobacter pylori* • hygiene hypothesis • immunology • regulatory T cells

The prevalence of asthma has steadily increased over the last few decades. Asthma is now the most prevalent chronic disease in childhood in developed countries, and approximately 300 million people suffer from this disease worldwide. The Global Initiative of Asthma defines asthma as a chronic inflammatory disorder of the airways. Chronic pulmonary inflammation is associated with airway hyper-responsiveness (AHR), which leads to the classical symptoms of asthma: recurrent episodes of wheezing, breathlessness, chest tightness and coughing [101]. The most common clinical phenotype is allergic asthma. In childhood, more than 90% of patients with severe asthma are allergic; among asthmatic adults, 60% are sensitized to common aeroallergens [1]. In allergic asthma, inflammation and airway obstruction are triggered by allergen exposure in atopic individuals. The pathophysiology underlying the disease is rather complex. Many studies suggest a genetic predisposition to the disease, and numerous asthma susceptibility genes have been identified. However, it seems that the individual contribution of these loci is relatively small [2]. Genetic changes are unlikely to account for the increase in allergic disease within a relatively short

time period, and simple genetic explanations for increased disease susceptibility have not been validated [3]. In recent years, increasing evidence suggests that lifestyle factors, such as nutrition, hygiene and exposure to environmental compounds, including tobacco smoke and microbial components, are important factors in determining asthma risk. These findings indicate that genome/environment interactions, which have also been proposed for other complex human diseases, play a pivotal role in the development of asthma [3]. Indeed, an urban lifestyle in early life increases the risk for asthma, suggesting that postnatal exposure to indoor antigens or urban pollutants might account for this effect. With regard to environmental factors influencing asthma development, studies focusing on farm environments and microbial exposure in early life have provided a major advance in understanding asthma. Indeed, children born and raised on farms have a much lower risk of allergy and asthma [4]. This effect is presumably associated with increased exposure to environmental microbes [5], suggesting that rural environments 'instruct' the infants' immune systems to be less susceptible to the development of allergies and asthma.

Pathophysiology of allergic asthma

The definition of asthma is rather broad, and various phenotypes of this complex syndrome are collectively referred to under the term 'asthma.' The diverse asthma phenotypes can be distinguished based on differing etiologies, immunological parameters or the clinical course of the disease [6,7]. It is not known whether the various forms of asthma-associated inflammation represent distinct pathophysiological phenotypes of the disease. Various approaches and strategies have been used to describe clinically meaningful phenotypes. The cellular assessment of sputum samples has led to the identification of patients predominantly exhibiting eosinophilia compared with patients with predominant neutrophilia and patients with a mixed inflammatory response. Patients with eosinophilic asthma exhibit a better response to treatment with inhaled corticosteroids compared with patients with predominant neutrophilic inflammation [8]. Furthermore, it has been possible to stratify patients based on gene expression profiles of bronchial epithelial cells. Patients with increased expression of Th2 cytokine (IL-4 and IL-13)-responsive genes (e.g., periostin) have been classified as 'Th2-high' patients in contrast to patients who do not show an increased expression of these genes and are therefore classified as 'Th2-low' patients [9]. 'Th2-high' patients respond better to inhaled corticosteroid therapy compared with 'Th2-low' patients [9]. Serum levels of periostin have further proven indicative of Th2-polarized inflammation in asthmatic patients, and high serum periostin levels accurately predict the response to monoclonal antibody therapy directed against IL-13 [10]. These results further suggest that detailed phenotyping of well-defined patient groups with asthma is useful and could potentially become a part of clinical routine [3].

The inflammatory processes underlying the development of allergic airway disease have been investigated in humans and also in animal models of the disease. Indeed, animal models of allergic airway disease have assisted us greatly in gaining a better understanding of the pathophysiological processes underlying asthma development. It is obvious that no single-animal model is suited to model all aspects of a disease as complex as human asthma. However, murine models have furthered the understanding of the different cell types and mediators involved in asthma development. Experimental findings support an important role of Th2 cells and Th2 cytokines (IL-4, IL-5 and IL-13) in the development of allergen-induced inflammation and AHR. Allergen-specific Th1 and Th17 cells have alternatively been implicated in promoting AHR and pulmonary inflammation, but appear to predominantly induce the influx of neutrophilic granulocytes into the lung [11,12]. Recently, IL-17 produced by Th17 cells has specifically been linked to allergen-induced AHR through direct effects on airway smooth muscle [13].

In recent years, more attention has focused on the initial events following allergen exposure. Indeed, exposure to allergens in combination with either exogenous or endogenous danger signals leads to activation of epithelial cells and the release of epithelial cytokines (IL-25, IL-33 and thymic stromal lymphopoietin) and chemokines [14]. These initial events recruit inflammatory cells from the circulation and induce the

activation and mobilization of dendritic cells (DCs). IL-33 in particular is a potent activator of mast cells and basophils and was recently described to activate innate lymphoid cells (ILCs) in conjunction with IL-25. ILCs comprise a heterogeneous family of innate hematopoietic cells that do not express surface markers of adaptive immunity and are not antigen restricted. Non-T, non-B cells expressing the transcription factor Id2 have been described in the mouse to produce type 2 cytokines. These cells have alternatively been called natural helper lymphocytes [15], multipotent progenitor type 2 cells [16], nuocytes [17] and innate type 2 helper cells [18] as they produce the Th2 cytokines IL-5 and IL-13 in response to IL-25 and IL-33. IL-9-producing ILCs have also been described [19]. The human cellular counterpart of murine ILCs has been identified in the lung, gut and nasal tissue [20,21]. These cells are also lineage marker negative but express the prostaglandin D2 receptor (CRTH2) and respond to IL-25 and IL-33 by production of IL-13 and IL-5 [20]. Pulmonary DCs that have encountered allergens in the lung migrate to the regional lymph nodes, where they are pivotal for the sensitization to inhaled allergens, and also trigger the influx of inflammatory cells following allergen contact in presensitized individuals [22]. IL-4 is required for Th2 polarization of T cells in the lymph nodes, and IL-4-competent T cells can subsequently differentiate into follicular helper cells or exit the draining lymph node into the circulation to become Th2 cells [14,23]. During allergic airway inflammation, Th2 cells accumulate in the airway tissue and secrete IL-4, IL-5 and IL-13 in an antigen-dependent manner. Whereas IL-5 is important for survival of eosinophils accumulating in the airways, IL-13 directly affects airway epithelial cells by inducing mucus and chemokine production and leading to alternative macrophage activation and smooth muscle alterations that result in AHR [24–26].

Microbial exposure & asthma

In recent decades, the incidence of asthma and associated allergic diseases has increased to epidemic proportions in developed countries, especially among children. As the rapid increase cannot readily be explained by changes in the gene pool, the growing prevalence of asthma has been attributed to exposure to external factors, such as pollution and tobacco smoke. One popular theory is the so-called 'hygiene hypothesis.' Human exposure to microbial antigens, especially during early childhood, has dramatically decreased due to changes in human ecology, including cleaner water and smaller families [27]. The hygiene hypothesis postulates that the increase of allergic disease is due to decreased sampling of microorganisms in food, air, water or soil [28]. Indeed, epidemiological studies have demonstrated an inverse association between asthma and hepatitis A, *Toxoplasma gondii* or herpes simplex virus I infection [29]. Furthermore, elegant studies of children in southern Germany have attributed the inverse correlation between asthma and growing up on a farm to the increased exposure to a wider range of microbes [4,5].

A second hypothesis, which has been put forward recently by Blaser and Falkow, is termed as the 'disappearing microbiota' hypothesis [27]. The fetus is sterile *in utero*; however, immediately

after birth and throughout life, humans are colonized by microorganisms that inhabit most exposed mucosal surfaces, including the nasal passages, the skin, mouth, vagina and gut [30]. Interestingly, the human intestine contains more than 100 trillion microorganisms that maintain a symbiotic relationship with the host. The genes of the microbial metagenome are estimated to outnumber the genes in the human genome by a factor of 100 [31]. This large and diverse population of microbes is the most important postnatal source of microbial stimulation of the immune system [32,33]. The exact composition of the gut microbiota is heavily influenced by host and environmental factors, such as time and type of delivery, hospitalization and breastfeeding experienced in the first year of life. Most individuals acquire a stable gut microflora resembling that of an adult during this period [33,34]. Studies in animals and humans have found an association between the gut microbiota and atopic disease [33]. Indeed, the complete absence of a commensal microbiota leads to exaggerated allergic airway disease in a murine model [35]. However, the intestinal mucosa is an immune-privileged site, which under normal conditions can tolerate exposure to a huge antigen load without resulting in inflammatory responses [36]. The mechanisms through which the gut microbiota influence specific aspects of the host immune response protecting against atopic diseases is not well defined. Commensal bacteria are thought to be involved in regulating the Th1/Th2 balance. In this concept, the absence of microbial colonization will result in predominant Th2 responses, as neonates are believed to be skewed toward a Th2-polarized response at birth [37]. By contrast, it is believed that exposure to gut microbial antigens stimulates the development of Th1 responses, thereby reducing the risk of Th2-driven atopic diseases and asthma [37]. An alternative explanation postulates that the intestinal microbiota is instrumental in driving differentiation of T cells into Tregs, which then produce anti-inflammatory cytokines such as IL-10 and TGF- β [30]. In the gut, DCs take up antigen and present it to naive T cells, which can then differentiate into either effector T cells or Tregs. Selective regulation of Toll-like receptor responsiveness may play a critical role in preventing mucosal DCs from mounting unnecessary inflammatory responses to commensal organisms [38]. Indeed, innate signaling pathways are instrumental in regulating tolerogenic functions of DCs. Lamina propria DCs respond to Toll-like receptor stimulation and produce IL-10 but little or no IL-12 [39,40]. DCs and macrophages in the lamina propria and in mesenteric lymph nodes share the ability to convert naive T cells into inducible Foxp3-positive Tregs via IL-10, TGF- β and retinoic acid secretion [41,42]. Lipopolysaccharide expressed by *Bacteroides* species is capable of inducing CD25 and Foxp3 expression in lamina propria lymphocytes [43], and polysaccharide A produced by *Bacteroides fragilis* is sufficient to induce the expansion of Tregs, which in turn results in protection not only against local intestinal inflammation but also against the development of autoimmune disease in other organs such as the CNS [44–46]. In a recent study, accumulation of invariant natural killer T cells in the gut and lung of germ-free mice was observed, which led to increased susceptibility to inflammatory bowel

disease or allergic airway disease [47]. In a second study, it was shown that alteration of commensal bacterial populations via oral antibiotic treatment resulted in elevated serum IgE concentrations, increased steady-state circulating basophil populations and exaggerated basophil-mediated Th2 cell responses and allergic inflammation [48]. These two recent studies report additional and/or alternative mechanisms through which commensal bacteria can influence immune responses and lend further support to the ‘disappearing microbiota’ hypothesis.

***Helicobacter pylori* & asthma: epidemiological evidence**

A specific component of the human microbiome, *Helicobacter pylori*, has received increasing attention recently due to its possible inverse association with asthma. *H. pylori* is the dominant bacterial species in its exclusive niche, the gastric mucosa [49,50], which differentiates the stomach from other microbial niches in the human body that house a large range of bacterial species as opposed to a single-dominant organism [27]. *H. pylori* has colonized the human stomach at least since the first human migration out of Africa more than 58,000 years ago [51]. *H. pylori* is prevalent in all adult populations [52], is typically acquired during the first years of life [53–55] and persists for a lifetime [56]. However, *H. pylori* infection rates in industrialized countries have declined with each successive generation in the last few decades, and human societies have moved from near-ubiquitous (>80%) *H. pylori* prevalence to infection rates in the single digits, at least among children, in the USA and western Europe (FIGURE 1) [27,57,58]. This development can be explained by the reduced prevalence of *H. pylori* in each new parent generation, which will decrease the potential for vertical transmission to the next generation in a stepwise manner [27,59]. Furthermore, diminished horizontal transmission resulting from changes in human ecology and behavior makes it more difficult to overcome losses in the vertical transmission [27]. Overall, the loss of *H. pylori* manifests as a birth cohort phenomenon [53]. Recent data from The Netherlands suggests a low-level consolidation of infection rates at approximately 10% in birth cohorts from 1993 to 2005 [60]. There is now mounting epidemiological data showing that the presence of *H. pylori* is associated with a decreased risk of developing asthma. In epidemiological studies, *H. pylori* antibody responses have mostly been measured to assess colonization. Indeed, *H. pylori*-specific antibodies are present for decades or even for life, consistent with the persistence of gastric colonization [61–63]. In epidemiological studies, increased serum IgE levels have been linked to patients lacking *H. pylori*-specific antibodies [64]. An additional epidemiological study assessed 7663 participants from the Third National Health and Nutrition Examination (NHANES III) trial. IgG serum antibodies against *H. pylori* and its virulence factor CagA were measured. CagA⁺ strains have been associated with a stronger inflammatory response in the stomach [65] and a stronger risk of gastric cancer development [66]. Interestingly, study subjects colonized with CagA⁺ *H. pylori* were less likely to have ever been diagnosed with asthma, and this association was particularly strong in patients with early-onset asthma [67]. *H. pylori* CagA⁺ status was also inversely associated with allergic rhinitis and other allergy symptoms [67]. An

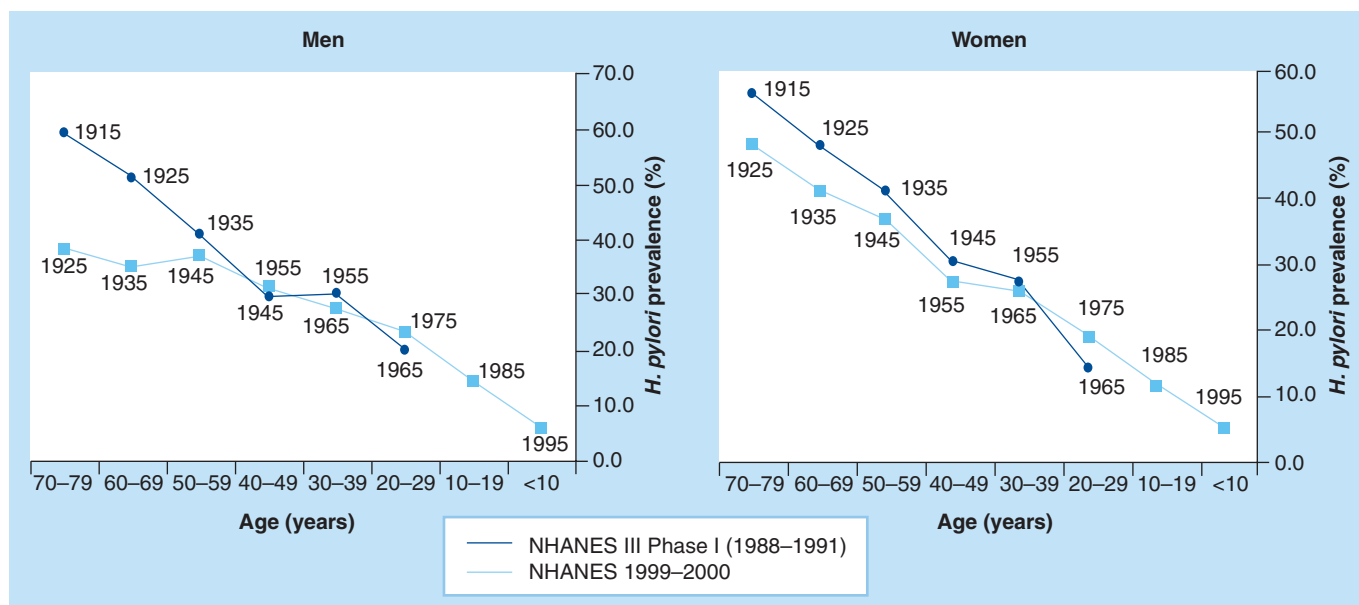


Figure 1. Prevalence of *Helicobacter pylori* positivity among men and women in the National Health and Nutrition Examination Survey.

Reproduced with permission from [57].

independent survey of 7493 participants of the NHANES IV trial with available *H. pylori* status revealed a similar association between *H. pylori* infection and asthma. A strong inverse relationship was detected between *H. pylori* infection and asthma onset before the age of 16 years [57]. A cross-sectional survey of adults from Sweden, Iceland and Estonia showed an inverse association of detected antibodies to *H. pylori* and prevalence of asthma and hay fever [68]. In a comparison of patient cohorts in Finland and Russia, *H. pylori* infection status statistically explained approximately half of the differences in the prevalence of atopy between the two populations [69]. The inverse correlation of *H. pylori* infection and asthma could further be confirmed in an urban population; the respective analysis of 318 asthmatic patients and 206 controls in New York City (NY, USA) demonstrated an inverse association between colonization of *H. pylori* and risk of asthma, particularly when examining individuals carrying CagA⁺ strains [70]. In contrast to these findings, some studies detected only weak [71-74] or no [75] associations between *H. pylori* infection and allergic disease or asthma. However, most of the negative studies were not adequately powered, and many of them did not separately assess CagA⁺ *H. pylori* infections. Taken together, there is accumulating epidemiological data demonstrating an inverse association between *H. pylori* infection and the development of asthma.

Mechanisms underlying the protective effects of *H. pylori*

Despite the compelling epidemiological evidence of a protective effect of *H. pylori* on asthma development, the mechanisms through which gastrointestinal immune responses to the pathogen translate into systemic anti-inflammatory or immunosuppressive effects have so far not been adequately described. As pointed out above, animal models of allergic airway disease have revealed some of the mechanisms underlying allergic sensitization and the development

of allergic airway disease. Similarly, a recently established mouse model of experimental *H. pylori* infection with a virulent patient isolate has facilitated studies investigating host immune responses to the pathogen and immunopathological consequences of chronic *H. pylori* infection. In this CagA⁺ *H. pylori* infection model, the infection-associated gastritis and development of gastric precancerous lesions faithfully recapitulate the gastric histopathology of a subset of *H. pylori*-infected patients [76]; infection of mice of various age groups further revealed a striking difference in disease outcome that depended on the age at the time of infection. Mice that had been infected during the neonatal period failed to control the infection and, as a consequence, were protected against the infection-associated immunopathology that is a hallmark of adult-infected animals [76]. Interestingly, in children infected with *H. pylori*, the level of gastritis is substantially reduced compared with adults. This reduction in inflammation has been linked to increased numbers of Tregs and higher levels of IL-10 and TGF- β in the gastric mucosa of infected children relative to adults, suggesting a predominantly regulatory response to the infection [77].

A possible inverse association between experimental infection with this patient isolate of *H. pylori* and asthma was investigated in murine model systems of allergic airway inflammation and AHR. Neonatal or adult mice were infected with *H. pylori* and subsequently sensitized using the model antigen ovalbumin. Sensitized mice develop airway inflammation, AHR and increased mucus production on challenge with the same antigen via the airways. In this model, infection with *H. pylori* significantly reduced AHR, evidenced by decreased airway resistance following metacholine challenge and alleviated peribronchiolar and perivascular inflammation and goblet cell metaplasia [78]. Pathogenic IL-5- or IL-17A-producing effector T cells in the lung were reduced as well. The strongest effect of the infection was observed in mice infected

during the neonatal period, whereas airway inflammation and AHR were only slightly reduced in adult-infected mice. The results imply a continuum of protection that is inversely correlated with age at the time of infection. The protective effect of *H. pylori* infection was abrogated when mice were treated with antibiotics after sensitization and prior to allergen challenge, suggesting that live bacteria need to be present to mediate this protective effect. Interestingly, the bacterial virulence factor CagA may not play the same pivotal role in mediating protection in the experimental model as in humans; an isogenic mutant lacking an essential component of the type IV secretion system required for CagA delivery to host cells was as effective as the corresponding wild-type strain at protecting from allergic airway disease.

Various pathophysiological pathways may contribute to the observed protection from allergic airway disease. One mechanism that has been proposed postulates that the induction of Th1 responses by *H. pylori* may prevent the development of allergen-induced Th2 responses through immune deviation. Experimental studies have assessed the potential of the *H. pylori* neutrophil-activating protein (NAP), which acts as an agonist for the TLR2 receptor in protection against asthma [79]. Indeed, peripheral blood monocytes from patients with allergies produce more IL-12 and TNF following incubation with *H. pylori* NAP. The administration of *H. pylori* NAP in models of allergic airway disease showed beneficial effects with respect to airway inflammation and Th2 cytokine production [80]. However, based on the observed protection of neonatally infected mice (which fail to generate pathogen-specific Th1 responses due to their development of immune tolerance to the bacteria), the authors suspected Treg responses to play a more important role. Indeed, increased numbers of pulmonary CD4⁺Foxp3⁺ Tregs were detected in the lungs of neonatally infected mice. Furthermore, the *H. pylori*-mediated protective effect could be abrogated by the systemic depletion of Tregs using an anti-CD25 monoclonal antibody during airway challenge. The hypothesis that *H. pylori*-mediated protection depends on Tregs was further strengthened by a set of adoptive transfer experiments. Noninfected mice injected with mononuclear cells isolated from the mesenteric lymph nodes of *H. pylori*-infected donors were protected with regard to asthma development. The prior depletion of Tregs in the infected donors abrogated protection and the direct transfer of mesenteric lymph node-derived CD4⁺CD25⁺ Tregs, but not CD4⁺CD25⁻ conventional T-cells, was sufficient to confer protection. Overall, these findings demonstrated in a preclinical model that *H. pylori* infection prevents allergic airway disease through the induction of Tregs. In addition, increased numbers of semimature DCs were detectable in the lungs of *H. pylori*-infected mice, which could potentially develop as a consequence of Foxp3⁺ Tregs aggregating with DCs, actively downregulating their costimulatory molecules and impairing the ability of the DCs to activate allergen-specific T cells (FIGURE 2) [81].

DCs induce Treg differentiation during *H. pylori* infection

DCs exhibiting a semimature MHCII^{hi}CD40^{lo}CD80^{lo}CD86^{lo} phenotype are believed to exhibit tolerogenic properties, which

allow them to convert naive T cells into Foxp3⁺ Tregs with suppressive activity [82]. Under these circumstances, Treg induction is achieved through antigen presentation in the absence of costimulatory signals or cytokines or in combination with the production of tolerogenic factors such as IL-10, TGF- β , retinoic acid and programmed death ligands [82,83]. Interestingly, *H. pylori* exposure of various DC populations has profound effects on these cells *in vitro* and *in vivo*. Indeed, *H. pylori*-experienced bone marrow- or mesenteric lymph node-derived DCs lose their ability to mature into fully immunogenic, stimulatory antigen-presenting cells and to activate effector functions in naive T cells. Instead, *H. pylori* exposure triggers tolerogenic properties in DCs, which become efficient inducers of Tregs *in vitro* and suppress *H. pylori* clearance and the associated immunopathology *in vivo* [84]. The precise mechanisms of the interaction between *H. pylori* and DCs triggering this tolerogenic/regulatory phenotype has not been completely unraveled. *H. pylori* is known to bind to DCs via the C-type-lectin DC-SIGN. Indeed, binding of *H. pylori* to DCs induced increased IL-10 production and prevented skewing of naive T cells to Th1 cells via DC-SIGN-dependent mechanisms [85]. Other studies investigating the direct interaction of DCs with *H. pylori* reported Treg skewing of naive T cells cocultured with *H. pylori*-exposed DCs. Interestingly, this effect was independent of the *H. pylori* virulence factors VacA and CagA but dependent on the cytokines TGF- β and IL-10 [86]. The predominantly tolerogenic role of DCs in the context of *H. pylori* infection is further evidenced by the observation that systemic DC depletion improves rather than abrogates the immunological control of *H. pylori* infection in experimentally infected mice and in mice challenged with live bacteria after *H. pylori*-specific vaccination [87]. DC depletion also breaks the immune tolerance to *H. pylori* that is acquired during neonatal infection [84], and results in reduced *H. pylori* colonization, stronger gastric Th1 and Th17 cell infiltration and more gastritis. Interestingly, *H. pylori*-exposed DCs were incapable of sensitizing mice to ovalbumin when administered intranasally, suggesting that *H. pylori*-mediated asthma protection is a direct consequence of the reprogramming of DCs *in vivo*. It is now widely accepted that DCs and Tregs regulate one another in a negative-feedback loop promoting a tolerogenic, immunosuppressive environment. One other novel finding was that the DC-derived cytokine IL-18 plays a crucial role in the tolerogenic activity of *H. pylori*-experienced DCs *in vitro* and *in vivo*. Indeed, DCs derived from IL-18-deficient donors did not induce Foxp3 expression in naive T cells on exposure to *H. pylori*. Furthermore, Tregs isolated from *H. pylori*-infected IL-18-deficient or IL-18 receptor-deficient mice were not capable of suppressing the development of allergic airway disease, nor did either strain develop immune tolerance to the infection. Additional cytokines, in particular IL-10 and TGF- β , are known to be involved in the induction of T-regulatory responses [86], and further studies are needed to determine in detail the signaling networks in T cells contributing to Treg differentiation on IL-18, IL-10 and TGF- β exposure. In summary, infection with *H. pylori* evidently results in the reprogramming of DCs toward a tolerogenic phenotype, which on the one hand ensures persistence of the bacteria in the

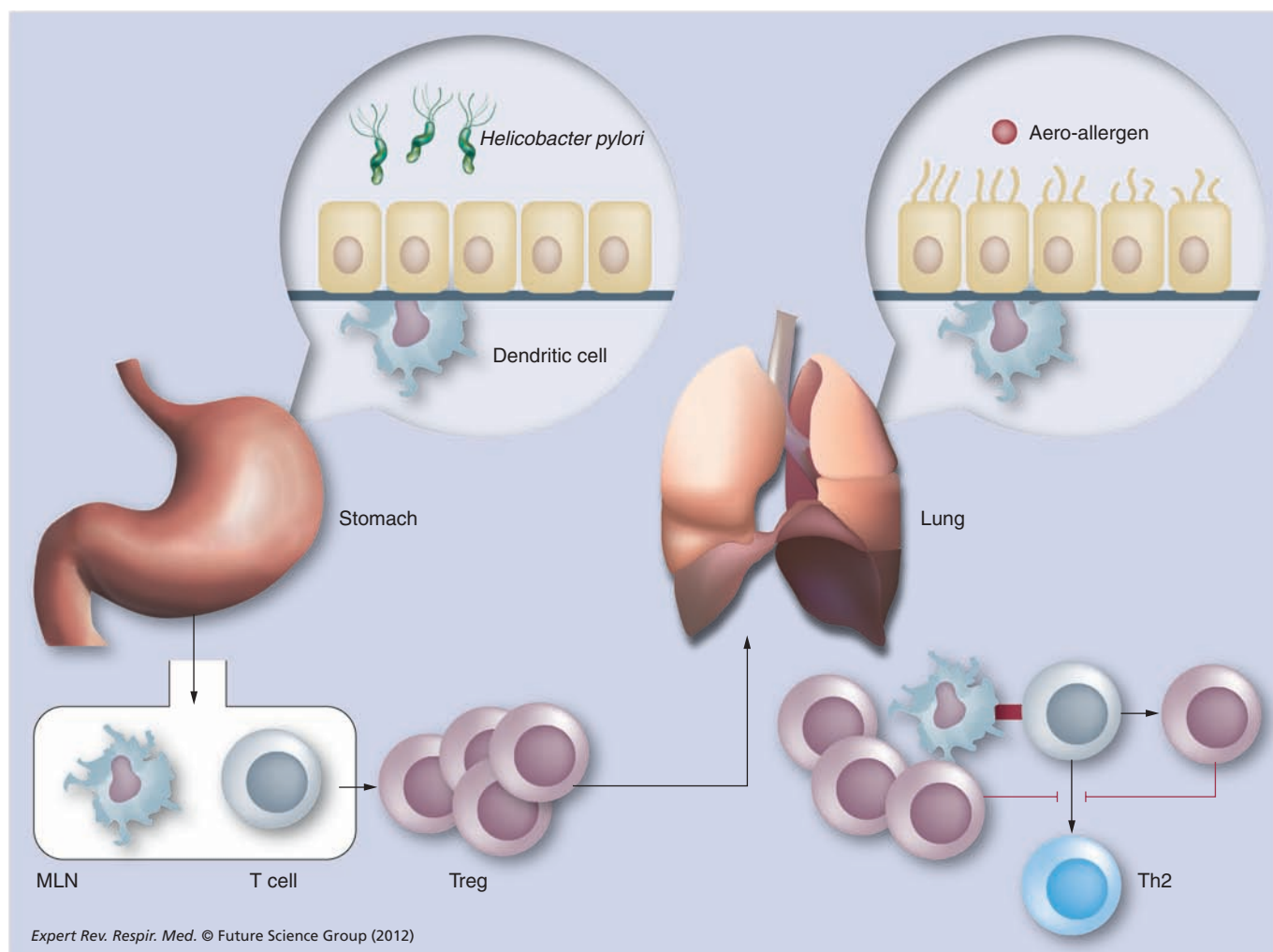


Figure 2. Mechanism underlying *Helicobacter pylori*-mediated suppression of allergic airway disease.

Helicobacter pylori infection in the stomach results in the induction of semimature dendritic cells, which migrate to regional lymph nodes and result in the induction of Tregs. Tregs inhibit allergic reactions in the lung either by directly affecting allergen-exposed dendritic cells or by inhibiting effector T-cell (Th2) responses.

MLN: Mediastinal lymph node.

host, and on the other hand may protect against allergic disease manifestations.

Expert commentary

Asthma prevalence is still rising, and despite the availability of symptomatic treatments for a large subset of the patient population, real advances in curing the disease have not been made. It is therefore necessary to further strengthen research efforts, which will improve our understanding of the disease and reveal innovative new treatment strategies. Indeed, epidemiological studies have pointed out a close association between the gradual disappearance of the gastric pathogen *H. pylori* from human populations and an increase in asthma incidence. *H. pylori* is unlikely to be the only environmental factor influencing asthma risk, although this association can be detected in highly diverse populations and geographical regions of the world. In analogy to the mechanistic studies that have been conducted to explain the beneficial effects of farm environments on asthma development, it will now be

imperative to work out the underlying immunological mechanisms and the bacterial factors involved in asthma protection. Recently, the first experimental evidence that *H. pylori* infection directly modulates DCs has been provided, by inducing their tolerance-promoting properties and thereby preventing pathogen- and allergen-specific T-cell activation. The further elucidation of the mechanistic underpinnings of asthma protection will advance our basic understanding of the disease.

Five-year view

We anticipate that experimental research will provide further insight into the interaction of *H. pylori* with the immune system and that the molecular and cellular mechanisms of *H. pylori*-mediated protection against allergic disease will be elucidated in great detail using a variety of model systems. By identifying the protective factor(s) of *H. pylori* contributing to DC reprogramming, Treg induction and asthma protection, it might be possible to develop novel strategies directed at asthma treatment and

prevention. It will be a formidable challenge for the future to identify the 'tolerance determinants' of the bacterium mediating this regulatory protective response. We expect that attenuated *H. pylori* or its components could potentially evolve into new treatment strategies, which in the future might allow a more immune-based treatment approach for patients with allergies and asthma.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Asthma prevalence is increasing worldwide.
- This rapid increase cannot be explained by changes in the gene pool, rather the growing prevalence of asthma is attributable to environmental and lifestyle changes.
- Two major hypotheses have been proposed: the hygiene hypothesis and the disappearing microbiota hypothesis. Hygiene hypothesis: due to changes in human ecology, the exposure to microbial antigens has been dramatically reduced resulting in increased asthma prevalence; the disappearing microbiota hypothesis: ecological changes affect the normal human microbial flora and result in increased asthma prevalence.
- Epidemiological data demonstrate an inverse association between *Helicobacter pylori* infection and the development of asthma.
- Experimental studies have begun to elucidate the mechanisms underlying asthma protection: *H. pylori* induces reprogramming of dendritic cells toward a tolerogenic phenotype, a mechanism that appears to protect against chronic inflammatory and allergic diseases.

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