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Role of infections in the induction and development of asthma: genetic and inflammatory drivers

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Abstract

Genetic and environmental factors interact to initiate and even maintain the course of asthma. As one of the highly risky environmental factors, infections in predisposed individuals can promote asthma development and exacerbations and/or prolong symptoms. This review will describe our current understanding of the genetic markers of innate immunity in the induction and development of asthma, the diverse roles of infections in modulating allergic inflammation, host susceptibility to infections and subsequent acute exacerbations in an allergic setting, and the therapeutic or preventive implications of existing knowledge. Current challenges and future directions in basic and clinical research of asthma are also discussed.

Keywords

airway inflammation; asthma; genetic variants; infection; innate immunity

What contributes to the induction & development of asthma?

Asthma is more like a multifactorial syndrome. Interactions of genetic and environmental factors are pivotal to determine asthma development. To date, more than 120 candidate genes of the innate and adaptive immune systems have been associated with asthma or atopy-related phenotypes [1,2]. Table 1 illustrates some of the factors involved in the induction of asthma, including infections and aeroallergen exposure and environmental tobacco smoke (ETS) exposure [3–26]. Among them, respiratory infections have been intensively investigated. As one of the highly risky environmental factors, infections in predisposed individuals can promote asthma development and exacerbations and/or prolong symptoms [9–20]. Other factors, such as ETS exposure, also contribute to asthma development. For example, prenatal maternal smoking, but not postnatal ETS exposure, has been associated with increased prevalence of physician-diagnosed asthma during childhood [21–24].

In this review, we will discuss the following:

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- The natural history of asthma
- Innate immunity and asthma pathogenesis
- The role of infections in airway allergic inflammation of asthma
- Allergic inflammation increasing host susceptibility to infections

Natural history of asthma

Long-term cohort studies on the natural history of childhood asthma show that most childhood asthma begins in infancy. Children usually have their first episode of wheezing before the age of 3 years, which is often associated with lower respiratory tract viral infections, such as infections with respiratory syncytial virus (RSV) and rhinovirus (RV) [27–34]. Children with RSV-induced bronchiolitis, compared with control subjects, are more likely to develop asthma symptoms with physician-diagnosed asthma within 12 months following the infection [33]. Furthermore, viral infection with respiratory symptoms during the first 2 years of life is a strong predictor of persistent wheezing observed during the third year of life [31,34]. Moreover, inhaled corticosteroid therapy in a maintenance phase of childhood asthma can only improve the symptoms, but may not alter asthma progression [35–37]. Although approximately two thirds of children with wheezing will have complete resolution of symptoms in adulthood, the remaining wheezing children develop persistent asthma symptoms in adulthood [38–43].

Patients with early-onset asthma (arbitrarily defined as onset before 12 years of age) have a significantly greater likelihood of allergic sensitization and clinical response to triggers (e.g., house dust mites and pollen) [5]. Early-onset asthma can be categorized into [44]:

- Transient wheezing
- Nonatopic wheezing in the toddlers and preschool-aged children
- IgE-mediated wheezing

However, this categorization is still debatable. Induction of asthma not only occurs early in life, but also occurs in adulthood. Adult-onset asthma is related to exposures to both allergic and nonallergic factors such as drugs, workplace substances (i.e., occupational asthma) or home environments. Nonallergic adult asthmatics often have a more-severe form of the disease [5, 45–48].

Innate immunity & asthma pathogenesis

Innate immunity is the first line of host defense against a variety of invading organisms and can interact with the adaptive immune system. With its constitutive expression, broad antimicrobial activity and instant availability, innate immunity provides great potential for fortifying host defense functions. Recently, genetic variations in innate immunity components have been shown to affect the host's capability to recognize microbes and subsequently influence the susceptibility to asthma development. Identification of genetic variants that alter the innate immunity is highly relevant to understanding asthma pathogenesis, and facilitates the development of novel preventive and therapeutic strategies.

Toll-like receptors (TLRs) are pattern-recognition receptors (PRRs) expressed in all barrier organs to recognize invading micro-organisms and to induce innate immune responses, and subsequent acquired immunity. In total, 11 human TLR genes and 13 mouse *TLR* genes have been identified [49,50]. Since 2004, several epidemiologic and genetic studies have found genetic associations between single nucleotide polymorphisms (SNPs) in TLRs and the prevalence of asthma, suggesting an impact of altered TLRs on the induction and perpetuation of asthma [51]. Some examples are provided in Table 2. Eder *et al.* have found genetic

variations in TLR2 as a major determinant of the susceptibility to asthma and allergies in children of European farmers. Farmers' children carrying a T allele in *TLR2*−16934, compared with children with genotype AA, were less likely to have a diagnosis of asthma (3 vs 13%; $p=0.012$), current asthma symptoms (3 vs 16%; $p=0.004$), atopic sensitization (14 vs 27%; $p=0.023$) and current hayfever symptoms (3 vs 14%; $p=0.01$) [52]. Hoffjan *et al.* have concluded that variations in TLR6 might play a role in the pathogenesis of childhood asthma, since, in a case–control study, they found a weak association between *TLR6* Ser249Pro polymorphism and asthma in German children. However, the significance was lost after Bonferroni correction [53]. By contrast, Tantisira *et al.* have reported that the variation of Ser249Pro in the *TLR6* gene is significantly associated with a decreased risk of asthma in African–Americans (odds ratio [OR]: 0.38; 95% confidence interval [CI]: 0.16–0.87; $p=0.01$) and a trend towards protection from asthma in European–Americans (OR: 0.72; 95% CI: 0.48–1.09; $p=0.12$) [54].

Considerable attention has been given to the potential role of TLRs in modifying the prognosis of asthma. TLR activation causes the release of effector molecules, such as cytokines and chemokines, which can modulate adaptive immune responses and subsequently influence the progression of asthma (Table 2). Recently, a case–control study in 1872 subjects (aged 9–11 years) investigated the putative functional genetic variants in ten human TLR genes for their association with different asthma phenotypes in children [55]. The study demonstrated that the protective effects of functional relevant TLR1, TLR6 and TLR10 variants (all capable of forming heterodimers with TLR2) are strongly associated with the development of childhood asthma. Significantly increased expression of *TLR1*, *TLR6* and *TLR10* mRNA has been found in individuals with the respective rare alleles. Furthermore, flow cytometry confirmed the increase of TLR1, TLR6 and TLR10 proteins on peripheral blood mononuclear cells (PBMCs) in the same group of patients. For the first time, they provided functional evidence that, after stimulation with specific TLR2/TLR1 or TLR2/TLR6 ligands, PBMCs from carriers of protective TLR1, TLR6 and TLR10 variants have augmented inflammatory responses (e.g., elevated levels of TNF- α), increased Th1 cytokine expression (e.g., IL-12 and IFN- γ) and reduced Th2 cytokine production (e.g., IL-4). These findings should lead to a better understanding of the protective mechanisms of microbial stimuli exposure against atopic sensitization and the subsequent development of asthma through TLR2 heterodimers in childhood. In addition, our recent mouse study has also shown that attenuation of TLR2-mediated innate immune responses by Th2 cytokines (IL-4 and IL-13) renders the allergic lungs more susceptible to respiratory *Mycoplasma pneumoniae* infection, suggesting that abnormal TLR2 signaling can affect the maintenance of asthma or its exacerbation with ensuing bacterial infections [56].

Toll-like receptor 4 is another important PRR extensively studied in asthma genetics. However, the association between the *TLR4* gene variants and asthma or asthma phenotypes is controversial. Most of the human genetic studies have shown no association of *TLR4* polymorphisms with the risk of developing asthma in both children and adults [52,57–59]. Conversely, Fagerås Böttcher *et al.* have found that the *TLR4* A896G polymorphism is associated with decreased LPS-stimulated IL-12 and IL-10 secretion and a fourfold increase in the prevalence of asthma, especially atopic asthma, in Swedish school-age children [60]. Sackesen *et al.* have reported that *TLR4* A896G and *TLR4* C1196T polymorphisms are associated with milder forms of disease in atopic asthmatics in Turkish children 6–18 years of age [61]. These data suggest that a polymorphism in *TLR4* modifies innate immune responses and the induction of asthma in children. It has been shown that TLR4 forms a complex with CD14 and MD2 on the surface of innate immune cells to induce the host response to lipopolysaccharide (LPS) during bacterial infections (Figure 1) [62,63]. The association of *CD14* polymorphisms with asthma development is suggestive and has not been fully replicated. The discrepancy of results eloquently demonstrates the intricate relationship between the

genome and the environment, and the complexity regarding their effects on disease. For example, some studies are in support of a protective role of *CD14* polymorphisms in allergy or asthma [64–68]. Baldini *et al.* have demonstrated that the *C159T* polymorphisms of the *CD14* gene are associated with elevated soluble CD14 levels and reduced serum IgE in children who are positive to common aero-allergens [64]. Bieli *et al.* have found a stronger protective role of farm milk consumption against allergic diseases in children carrying the A allele in *CD14* 1721 than in children homozygous for the G allele, which might be mediated through farm milk-induced *CD14* gene expression [67]. However, equally impressive evidence against an association between *CD14* polymorphisms and protection against allergy or asthma also exists [69–71]. The opposite results are observed not only in different populations but also within the same population with different levels of microbial exposure. These apparently inconsistent results may simply reflect random findings in underpowered studies. However, an alternative explanation is that these findings represent a consistent but complex gene–environment interaction. One research group has proposed the endotoxin switch theory, where the C allele confers a risk at low exposures of LPS while the T allele confers a risk at high exposures of LPS, and this may account for apparent inconsistencies among studies [72]. Therefore, we should be aware that genes and environmental factors are intertwined in complex, nonlinear relationships, such that the same genetic background might result in the expression of different phenotypes in different environments. A reasonably full understanding of gene–environment interactions requires epigenetic as well as classical genetic mechanisms to be taken into account.

In addition, some other genetic factors may modulate the immune responses to infections and, consequently, influence the pathogenesis of asthma (Table 3). Janssen *et al.* have found that SNPs in other innate immune genes, such as vitamin D receptor (*VDR*), *JUN*, *IFN- α 5* and nitric oxide synthase (*NOS*)-2A, are also important in determining host susceptibility to RSV-induced bronchiolitis, which in turn affects the inception of asthma after RSV infection in childhood [73]. Mannose-binding lectin (MBL), one of the PRRs, initiates complement deposition on microbial surfaces and is associated with severe respiratory infections. Low mannose-binding lectin (MBL) expression associated with variation in the *MBL2* gene promoter region is shown to be a significant risk factor for asthma in nonatopic Finnish adult males [74]. Also, *MBL2* polymorphisms are weakly associated with asthma and atopy in Chinese children [75]. However, Müller *et al.* have reported conflicting results regarding the potential role of MBL deficiency in the development of asthma, since they did not observe any association of *MBL2* genotypes with atopy-related phenotypes, such as asthma, allergic rhinitis, atopic dermatitis and allergic sensitization, in German children. They presume that previous data are not corrected for multiple testing due to the small size of the subgroup [76]. Recently, a novel innate immunity gene, myosin light chain kinase (*MYLK*), has been speculated as a viable candidate gene for asthma. *MYLK* gene polymorphisms are related to severe asthma phenotypes in African–Americans, which may offer a genetic explanation as to why more-severe asthma phenotypes are observed in this population [77–79]. In addition, defensins are small endogenous antimicrobial peptides that serve as pivotal components of innate immunity. Recent studies have shown that specific SNPs in the human β -defensin 1 (*DEFB1*) locus are associated with asthma and atopy. Levy and colleagues have found that the genomic SNP T1816C and the intronic SNP IVS+692 in the *DEFB1* gene are significantly over-represented among asthma cases in two Caucasian cohorts [80]. Leung *et al.* have reported that asthma diagnosis and atopy are more common in Chinese children with minor alleles G20A and G52A in the *DEFB1* gene, who also have higher total IgE levels in their plasma [81].

In summary, increasing numbers of studies suggest that alterations in innate immunity genes affect both asthma inception and development. However, research findings are not consistent among different research studies, possibly due to the small sample sizes and the lack of functional studies. Future studies should focus on specific gene–environment interactions in

relation to asthma instead of general genetic studies. More independent replications in various populations, such as longitudinal birth cohort or follow-up studies, are needed to confirm the importance of a candidate gene in asthma. More importantly, epidemiological, clinical and animal studies should be performed in a systematic manner to determine the role of gene products in asthma pathogenesis once a gene has been replicated. For example, augmented expression of *MYLK* has also been observed in bronchial biopsies of severe-persistent asthmatics [77]. However, its function in asthma (e.g., phenotypes, gender differences, action in inception or maintenance phase and whether it is good or bad for airway inflammation) remains largely unknown.

Role of infections in airway allergic inflammation of asthma

The chronic inflammatory response in the airways of asthmatics may be persistent even in the absence of allergens and is skewed towards a Th2 immune response, involving CD4⁺ Th2 cells, eosinophils, mast cells and the Th2 cytokines IL-4, IL-5, IL-9 and IL-13 [82]. Microbial infections could result in a predominant Th2 or Th1 response that exacerbates or attenuates asthma, respectively. Both viral and bacterial infections are able to modify the Th2 and Th1 response.

Respiratory syncytial virus & rhinovirus

Certain viral infections are highly associated with asthma prevalence in children [12–19,27–34]. Wu *et al.* have, for the first time, provided evidence to suggest a causal role of viral infections in asthma inception [20]. RSV is the major cause of infant lower respiratory tract infections. Infection with RSV in early life is associated with the induction of post bronchiolitis wheezing that may progress to asthma in childhood [27]. Children with persistent episodes of wheezing at 6 years of age have been shown to experience a higher prevalence of asthma with poor lung function and elevated serum IgE levels [33]. In the last few years, RV is increasingly being shown to be as important as RSV in inducing acute episodes of wheezing in infancy. Gern *et al.* have found that RV infection induces a relatively weak Th1 response with a low IFN- γ /IL-5 ratio in the sputum, which is inversely related to both peak cold symptoms and the time to clear the virus [83]. Furthermore, RV-associated wheezing is significantly associated with atopy [84]. Results from the recent Childhood Origins of Asthma (COAST) cohort study suggest that wheezing following RV infection in infancy and early childhood is the most significant predictor for the subsequent development of asthma at 6 years of age. From birth to 3 years of age, wheezing with infection by RSV, RV, or both, is associated with an increased risk of asthma at 6 years of age. Nearly 90% of children with RV-induced wheezing in the third year of the study are later diagnosed with asthma at 6 years of age [19]. Notably, the age at the first infection is an important factor in determining the nature of immune responses to the virus. RSV-positive infants younger than 3 months of age are found to have higher levels of IL-4 than healthy controls and RSV-positive infants older than 3 months of age. These data suggest that the first infection in younger infants has been associated with Th2 responses [85], which have been clearly reproduced in mouse models [86]. Collectively, Th2 immune responses in early infancy following severe acute RSV or RV infections may simply serve as a marker for those genetically predisposed individuals to develop asthma in later life.

Besides their role in the inception of childhood asthma, RSV and RV infections also contribute to the exacerbation of established asthma using various mechanisms, such as the induction of a Th2 response (Figure 2) [87]. Viremia during RV respiratory infections is rather common in the early phase of acute asthma exacerbations and is related to exacerbation severity [88]. Following exposure to RV, PBMCs from asthmatic subjects produce significantly lower levels of IFN- γ and IL-12, but higher levels of IL-4 [89]. In addition to their effects on Th2 and Th1 cytokine production, viruses may utilize other mechanisms to promote asthma exacerbations. For instance, infection latency of RSV or adenovirus likely causes persistent infection, thus

contributing to exacerbations of chronic lung diseases including asthma [90,91]. Additionally, viral infections induce mediators from airway epithelial cells to modify allergic inflammation. Thymic stromal lymphopoietin (TSLP) is an important factor to trigger dendritic cell-mediated Th2 responses. TSLP expression has been induced in human airway epithelial cells following *in vitro* infection with RV and *in vitro* stimulation with a TLR3 ligand (dsRNA). These results imply that respiratory viral infection may directly amplify Th2 inflammation in asthmatic airways via the induction of TSLP [92]. Thymus and activation-regulated chemokine (TARC), another Th2 chemokine from airway epithelial cells, is increased in asthmatic airways and correlated with eosinophils and IL-5 and IL-13 levels [93–97]. Recently, it has been found that RSV and IL-4/IL-13 synergistically increase TARC production in human lung epithelial cell lines, which further explains the role of viral infections in asthma exacerbations [98]. In addition, RV infection typically causes the influx of eosinophils into the airways and airway hyperactivity in allergic patients, in part through virus-induced eosinophil peroxidase (EPO) production [99]. Previous studies have shown that the production of type I interferons (IFN- α/β) and type III interferons (IFN- λ s), the important effectors in innate host defense against viral infections, are deficient in asthmatic cells [100–102]. Recently, Wark *et al.* have shown that IFN- γ -induced protein 10 (IP-10) is released from bronchial epithelial cells (BECs) after RV infection, suggesting that it could be used as a specific marker to predict virus-induced asthma exacerbations [103]. RV infection induces the production of VEGF, the major mediator of angiogenesis, in primary airway epithelial cells and fibroblasts, which may be associated with airway modeling and asthma persistence [104–106].

Bacteria & their components

As with viral infection, certain bacterial infections may also positively contribute to asthma inception. For example, neonates colonized in the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* or a combination of these organisms are shown to have an increased risk of recurrent wheezing and asthma in early life [107]. However, a protective role of bacteria and their components in the development of asthma has also been reported [108]. Some studies have shown that Bacillus Calmette-Guérin (BCG) vaccination or mycobacterial exposure is inversely associated with atopy or airway allergic inflammation [109–111]. For instance, positive tuberculin responders in BCG-vaccinated children have a lower incidence of asthma, lower levels of serum IgE and Th2 cytokines IL-4, IL-10 and IL-13, and higher levels of the Th1 cytokine IFN- γ [109]. A single injection of heat-killed *Mycobacterium vaccae* (SRL172) in atopic asthmatic patients has been shown to reduce allergen-induced airway responses, including FEV₁, serum IgE and IL-5 levels [110]. Furthermore, induction of Tregs following administration of heat-killed *M. vaccae* (SRL172) or BCG may confer protection against airway allergic inflammation in mice, in part through the production of IL-10 and TGF- β [112,113]. However, other studies report that mycobacterial exposure or BCG vaccination is not associated with atopy and asthma [114–116]. Therefore, it is worth mentioning that the relationship between atopy and mycobacterial exposure or BCG vaccination in early life still remains debatable.

Recent clinical and animal studies strongly support a role of microbial components in modulating airway allergic inflammation. Most microbial components have been shown to activate innate immunity such as TLR signaling pathways. Endotoxins are lipopolysaccharide components of the outer membranes of Gram-negative bacteria. Increased levels of endotoxins in house dust are associated with more asthma symptoms and worse lung function [117–119]. Despite these adverse effects, early exposure to endotoxins may reduce future allergies or asthma [120]. Peptidoglycan is a major component of the cell wall of Gram-negative and Gram-positive bacteria in the environment. Muramic acid, a constituent of peptidoglycan, is inversely associated with wheezing in children [121].

Among the microbial components that regulate allergic inflammation, TLR9 agonists unmethylated cytosine-phosphate-guanosine (CpG) dinucleotide motifs in bacterial DNA and their synthetic products (CpG-ODNs) have been extensively investigated. Clinical trials using CpG DNA appear to be promising since the treatments improve asthma symptoms [122–124]. As for the involved mechanisms, CpG-ODN mediates protection against allergic inflammation in mice through p38 MAP kinase-dependent IL-12 production by alveolar macrophages [125]. Moreover, a single treatment with a CpG-containing immunostimulatory DNA sequence (ISS) administered before allergen challenge in mice inhibits the Th2 response by blocking antigen presentation to Th2 cells from lung antigen-presenting cells (APCs) due to reduced expression of costimulatory molecules. Moreover, ISS reduces IgE-dependent release of Th2 cytokines, especially IL-4, from basophils and/or mast cells in the airways of Th2-primed mice [126]. Recently, Ashino S *et al.* revealed that IFN- α , IFN- β and IL-12, but not IFN- γ , are required for the inhibitory effect of CpG-ODN in allergic inflammation in mice [127].

All of these findings suggest that microorganisms or their components have the potential to treat asthma by altering the Th1 and Th2 responses. However, their efficacy in treating asthma depends on a number of factors including timing, dose, anatomical site and duration as well as host characteristics such as genetic susceptibility and nutritional status [128]. For example, microbial exposure level is an important factor in determining the type of inflammatory response and the subsequent effects on asthma prevalence. Inhaled LPS triggers Th2 responses at a very low level and acts as an adjuvant for Th2 sensitization. However, when LPS is inhaled at higher doses (i.e., 1000-fold higher than the Th2-promoting ones), it induces Th1-biased responses and prevents eosinophilic airway inflammation in allergic mice [129]. In addition, timing of the infections in relation to allergen challenges also determines the effect of a given infection on asthma. A growing body of basic and clinical literature implicates the atypical bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* as potentially important factors in asthma, although their exact contribution to asthma development and/or persistence remains uncertain [10,130–132]. Our previous studies in mouse models have clearly shown that *M. pneumoniae* infection prior to allergen exposure is protective against allergic responses, including decreased AHR, lung inflammation and IL-4 production, and increased IFN- γ production. By contrast, if the infection occurs after allergen exposure, *M. pneumoniae* infection enhances allergic responses [133]. Similarly, CpG inhibits airway eosinophilia and Th2 cytokine production in antigen-sensitized mice only when CpG is administered simultaneously with or in advance of an antigen challenge [134].

Fungi

Fungi are known to be causative factors in inducing asthmatic symptoms and contribute to asthma severity. Outdoor airborne fungi (e.g., *Cladosporium*, *Altearnaria*, *Penicillium* and *Aspergillus*) and indoor fungi (e.g., *Aspergillus*, *Neurospora* and *Eurotium*) are significant triggers of IgE formation and inflammatory cytokine production [135,136].

Parasites

To date, there is no strong evidence that parasitic infections contribute to the inception of asthma. However, certain parasites may protect people against established asthma and allergies, especially for individuals living in endemic areas [9,137–140]. Surprisingly, although parasites and asthma are both associated with a Th2 immune response, and acute parasitic infections may increase manifestations of allergy, multicellular parasites (e.g., helminth worms) can decrease allergic inflammation. Multicellular parasites have evolved sophisticated strategies for long-term immune evasion, including induction of natural suppressive mechanisms such as Tregs. Thus, immune components derived from helminth worms may have anti allergic effects and could serve as an alternative approach to treat asthma.

In summary, more evidence has shown that infections play important roles in the induction and development of asthma. However, the precise mechanisms need to be elucidated to validate the use of microbial components or even the microorganism itself in asthma therapy.

Allergic inflammation increases host susceptibility to infections

Previous work has centered on the impact of respiratory infections on asthma exacerbations or allergic responses. Recently, studies have begun figure out the impact of allergic inflammation on asthmatic susceptibility to infections. An important research question is: does the established airway allergic inflammation compromise host innate immunity to hinder the elimination of an infectious organism? Emerging pieces of evidence have confirmed the regulatory role of established airway allergic inflammation in host innate immunity to respiratory infections. Host defense, especially innate immunity, against typical bacteria (e.g., *Staphylococcus aureus* and *Pseudomonas aeruginosa*) and atypical bacteria (e.g., *M. pneumoniae* and *C. pneumoniae*) can be inhibited by allergic inflammation in humans and mice. Some human studies have suggested that deficient expression of antimicrobial peptides (e.g., LL-37 and β -defensins 2 and 3) may account for the increased susceptibility to *S. aureus* infection in patients with atopic dermatitis [141,142]. Our recent work also suggests that the short palate, lung and nasal epithelium clone 1 (SPLUNC1) protein serves as a novel host defense protein against *M. pneumoniae* and that an allergic setting markedly reduces SPLUNC1 expression, which may in part contribute to the persistent nature of bacterial infections in allergic airways [143]. However, the molecular mechanisms involved still remain unclear. Lately, we have found that the established ovalbumin-induced allergic airway inflammation, or the prominent Th2 cytokines IL-4 and IL-13, reduces *M. pneumoniae*-induced TLR2 expression and subsequent production of IL-6, and eventually impairs *M. pneumoniae* clearance from the allergic lungs [56]. This cascade is partly mediated by inhibition of NF- κ B activation through the STAT6 signaling pathway. It indicates that attenuation of TLR2-mediated innate immune responses by Th2 cytokines renders the allergic lungs more susceptible to respiratory bacterial (i.e., *M. pneumoniae*) infections.

Future clinical and animal studies are warranted to explore the underlying molecular mechanisms of the interactions between infections and asthma in order to identify novel targets for the prevention and treatment of asthma.

Conclusion

Genetic and environmental factors, including infections, interact to initiate and even maintain the course of asthma (Figure 2). Generally, allergens and certain respiratory infections may initiate asthma in genetically susceptible individuals or exacerbate existing asthma. By contrast, some infectious agents can protect against asthma. More epidemiological, clinical and animal studies must be performed in order to explore the underlying molecular mechanisms of the interactions between infections and asthma. Ultimately, this may help identify novel, effective therapies and prevent the induction and development of asthma.

Expert commentary & five-year view

The most efficient and cost-effective approach to prevent asthma inception or development is probably to reduce or avoid exposure to environmental agents that are known to be detrimental to asthma. For example, in 'high-risk' infants, prevention of allergen exposure, respiratory infections and passive tobacco smoking is recommended.

Although novel information is being gained from the existing genetic and epidemiological studies, several limitations in the current literature must be addressed to better understand the role of infections in the induction and development of asthma. It is clear that multiple genetic

factors and environmental factors interact and eventually determine the overall risk of asthma in individuals. Thus, to decipher the exact role of a gene (or genes) that has been replicated through gene–gene and gene–environment studies in diverse populations (e.g., children vs adults), with larger sample sizes, immediate epidemiological, clinical and animal studies should be performed in a systematic manner. This may be challenging, but will reveal the functional consequences of the involved gene(s).

Because of their multifactorial nature, to date, there is no single regimen that can be used to prevent or treat asthma and allergies. Thus, we should rigorously perform mechanistic and functional clinical and animal studies to speed up the development of personalized medicine that specifically identifies the genetic (e.g., innate immune genes) and environmental (e.g., infections) risk factors responsible for the induction and maintenance of asthma. Although a personalized cure is unlikely to be developed in the next few years, with improved knowledge of the development of detailed asthma phenotypes and underlying mechanisms, patient-specific treatments are emerging [144]. For example, since genetic variations in children, such as polymorphisms of *TLR4*, have been shown to be associated with the susceptibility to respiratory viral infection and an increased risk of the later development of asthma, children with *TLR4* mutations would be good candidates for viral vaccination or treatment with an anti-RSV antibody (e.g., motavizumab) to prevent viral infections and the ensuing RSV-related asthma or acute exacerbation [145–147]. Moreover, although some safety concerns still need to be addressed (e.g., as possible side effects, including local inflammatory responses), administration of exogenous type I IFN- α/β or type III IFN- λ s may be a novel approach to treat or prevent asthma exacerbations caused by certain respiratory viral infections. In addition, the new approaches to introduce immunomodulatory compounds derived from infectious agents, such as mycobacteria, helminths and bacteria, are very promising for future clinical applications. CpG derivatives are currently being evaluated as a novel therapeutic agent for the treatment of allergic diseases, including asthma. Some helminthic substances have anti-allergic effects, and may become useful as therapeutic modalities for many atopic and allergic disorders such as asthma.

We believe that the following emerging challenges in asthma research and practice are attainable in the next 5 years:

- The identification of all asthma-associated genes;
- An understanding of the role of epigenetics in the induction and maintenance of asthma;
- Asthma phenotyping based on combinational approaches of genetics, epigenetics and environmental risk factors. In a few years, we will be able to access the data from the NIH Human Microbiome Project to better define the role of infections in asthma pathogenesis;
- The development of methods to modify the gene functions at the epigenetic and post-transcriptional levels in order to correct or compensate for the abnormalities in genes associated with asthma induction.

Key issues

- Genetic and environmental factors interact to initiate and maintain the course of asthma.
- Genetic variations in innate immunity components, such as Toll-like receptors, have been shown to be responsible for the varying degree and/or pattern of host recognition of microbes and, subsequently, disease progression or regression.

- Infections in predisposed individuals can promote asthma development and exacerbations and/or prolong symptoms.
- Infections can also repress asthma depending on a number of factors, including timing and dose.
- The established airway allergic inflammation dampens host innate immune responses to respiratory infections.
- Because of the multifactorial nature of asthma, there is no single regimen that can be used to prevent or treat the disease.
- Mechanism-directed therapeutic approaches are needed to prevent or cure asthma.
- The new approaches to introduce immunomodulatory compounds derived from infectious agents, such as bacteria (CpG motifs), mycobacteria and helminths, are very promising for future clinical applications.
- Limitations of current studies and future challenges must be addressed to better understand the role of infections in the induction and development of asthma.

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Figure 1. Th2 response is enhanced by viral or bacterial infections through TLR signaling pathways
 AP: Activator protein; MD: Myeloid differentiation protein; MyD88: Myeloid differentiation factor 88; NF-κB: Nuclear factor-κB; TARC: Thymus activation-regulated cytokine; TIRAP: Toll-interleukin 1 receptor domain-containing adaptor protein; TLR: Toll-like receptor; TRAM: Transverse rectus abdominis musculocutaneous; TRIF: TIR domain-containing adaptor protein inducing IFN-β; TSLP: Thymic stromal lymphopoietin.

Figure 2. Interactions of genetic and environmental factors play pivotal roles in the induction and maintenance of asthma

ADAM33: A disintegrin and metalloprotease 33; CpG DNA: Cytosine-phosphate-guanosine DNA; IL-4R α : IL 4 receptor- α ; RSV: Respiratory syncytial virus; RV: Rhinovirus; TLR: Toll-like receptor.

Table 1

Environmental risk factors involved in the induction of asthma.

Risk factors	Association with asthma	Ref.
<i>Allergens or irritants</i> House dust mites, pollen, molds, pet danders, cockroaches, fossil fuels and fungi	Allergic asthma can develop at any age, although it commonly begins in early childhood	[3–8]
<i>Respiratory viral infections</i> Respiratory syncytial virus, rhinovirus and other viruses (e.g., parainfluenza, influenza A and metapneumovirus)	Respiratory viral infections are strongly associated with wheezing episodes in infants and young children, and may contribute to the induction and exacerbation of asthma	[9–20]
<i>Others</i> Air pollutants (e.g., environmental tobacco smoke exposure)	Prenatal maternal smoking, but not postnatal environmental tobacco smoke exposure, has been associated with an increased prevalence of physician-diagnosed asthma during childhood	[21–24]
Medication (e.g., aspirin)	The prevalence of aspirin-induced asthma in the adult asthmatic population is approximately 4–10%	[25]
Obesity	Epidemiologic studies have suggested that overweight and obesity increase asthma incidence	[26]

Table 2

Single nucleotide polymorphisms in Toll-like receptor genes and their association with asthma.

TLR	Ligands	Association with asthma	Ref.
<i>TLR1</i>	Heterodimerizes with TLR2 to recognize bacterial proteoglycans	<i>TLR1</i> 2192T and <i>TLR1</i> 743A polymorphisms are strongly associated with asthma development in children from Munich and Dresden	[55]
<i>TLR2</i>	Bacterial proteoglycans (e.g., lipoteichoic acids and peptidoglycan)	<i>TLR2</i> 16934T polymorphism is associated with decreased asthma symptoms, prevalence and atopy in children of European farmers	[52]
<i>TLR4</i>	Bacterial LPS and lipoteichoic acids	Most of the human genetic studies have shown no association of <i>TLR4</i> polymorphisms with the risk of developing asthma in both children and adults The <i>TLR4</i> A896G polymorphism is associated with decreased LPS-stimulated IL-12 and IL-10 secretion and a fourfold increase in the prevalence of asthma, especially atopic asthma, in Swedish children <i>TLR4</i> A896G and <i>TLR4</i> C1196T polymorphisms are associated with milder forms of disease in atopic asthmatics in Turkish children	[52,57–59] [60] [61]
<i>TLR6</i>	Heterodimerizes with TLR2 to recognize bacterial proteoglycans	A weak association is found between <i>TLR6</i> S249P polymorphism and asthma in German children. However, the significance is lost after Bonferroni correction <i>TLR6</i> S249P polymorphism is significantly associated with decreased risk for asthma in African-Americans and a trend towards protection from asthma in European-Americans <i>TLR6</i> 2078T and <i>TLR6</i> 745C polymorphisms are strongly associated with asthma development in children from Munich and Dresden	[53] [54] [55]
<i>TLR10</i>	May heterodimerize with TLR1 or TLR2 to recognize bacterial proteoglycans	<i>TLR10</i> 2323A polymorphism is possibly associated with asthma development in children from Munich and Dresden	[55]

LPS: Lipopolysaccharide; TLR: Toll-like receptor.

Table 3

Single nucleotide polymorphisms in innate immunity genes and their association with asthma.

Genes	Association with asthma	Ref.
<i>TLR</i>	See details in Table 2	
<i>MBL</i>	Low MBL expression associated with variation in the <i>MBL2</i> gene promoter region is shown to be a significant risk factor for asthma in nonatopic Finnish adult males	[74]
	<i>MBL2</i> polymorphisms are weakly associated with asthma and atopy in Chinese children	[75]
	No association has been found between <i>MBL2</i> genotypes and atopy-related phenotypes, such as asthma, allergic rhinitis, atopic dermatitis and allergic sensitization, in German children	[76]
<i>MYLK</i>	<i>MYLK</i> gene polymorphisms are related to severe asthma phenotypes in African-Americans	[77–79]
<i>DEFB1</i>	The genomic SNP T1816C and the intronic SNP IVS+692 in the <i>DEFB1</i> gene are significantly over-represented among asthma cases in two Caucasian cohorts	[80]
	Asthma diagnosis and atopy are more common in Chinese children with minor alleles for G20A and G52A in the <i>DEFB1</i> gene who also have higher total IgE levels in the plasma	[81]
Others (e.g., <i>VDR</i> , <i>JUN</i> , <i>IFN-α5</i> and <i>NOS2A</i>)	SNPs in other innate immune genes are also important in determining host susceptibility to RSV-induced bronchiolitis, which in turn affects the inception of asthma after RSV infection in childhood	[73]

DEFB1: β-defensin 1; MBL: Mannose-binding lectin; MYLK: Myosin light-chain kinase; NOS2A: Nitric oxide synthase 2A; RSV: Respiratory syncytial virus; SNP: Single nucleotide polymorphism; TLR: Toll-like receptor; VDR: Vitamin D receptor.