The Protective Effects of Helicobacter pylori Infection on Allergic Asthma

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Abstract

As an ancient Gram-negative bacterium, Helicobacter pylori has settled in human stomach. Eradicating H. pylori increases the morbidities of asthma and other allergic diseases. Therefore, H. pylori might play a protective role against asthma. The “disappearing microbiota” hypothesis suggests that the absence of certain types of the ancestral microbiota could change the development of immunology, metabolism, and cognitive ability in our early life, contributing to the development of some diseases. And the Hygiene Hypothesis links early environmental and microbial exposure to the prevalence of atopic allergies and asthma. Exposure to the environment and microbes can influence the growing immune system and protect subsequent immune-mediated diseases. H. pylori can inhibit allergic asthma by regulating the ratio of helper T cells 1/2 (Th1/Th2), Th17/regulatory T cells (Tregs), etc. H. pylori can also target dendritic cells to promote immune tolerance and enhance the protective effect on allergic asthma, and this effect relies on highly suppressed Tregs. The remote regulation of lung immune function by H. pylori is consistent with the gut-lung axis theory. Perhaps, H. pylori also protects against asthma by altering levels of stomach hormones, affecting the autonomic nervous system and lowering the expression of heat shock protein 70. Therapeutic products from H. pylori may be used to prevent and treat asthma. This paper reviews the possible protective influence of H. pylori on allergic asthma and the possible application of H. pylori in treating asthma.

Introduction

Since Gram-negative Helicobacter pylori was discovered, the relationship between H. pylori infection and asthma has gradually attracted people’s eyes. Kalach et al. [1] analyzed the infection of H. pylori in adults and chil-
Children from the perspective of host response, epidemiology, related diseases, clinical features, therapies, and diagnosis. The incidence of *H. pylori* infection is decreasing in both adults and children in developed countries and several developing areas, which is opposite from the increased incidence of asthma in children and other allergic disorders. Ness-Jensen et al. [2] found that *H. pylori* infection has been related to a 40% decrease of asthma in those who are below the age of 18 years with abdominal obesity. A recent study found that 16.4 percent of children who were negative for *H. pylori* at the age of 2 and 10 had asthma at the age of 16, but if they were positive for *H. pylori* at the age of 12, they did not have asthma at the age of 16. It is suggested that the early exposure to *H. pylori* can prevent asthma [3]. Fouda et al. [4] used ELISA for determination of *H. pylori* IgG in the serum of asthma and healthy children. The results showed that the titer of IgG was negatively correlated with the degree of asthma. Serum *H. pylori* could prevent asthma in children and was inversely correlated with the severity of asthma. Accumulating evidence suggested that the infection of *H. pylori*, particularly CagA-positive *H. pylori*, was negatively correlated with the development of asthma. A study of Greek children has also proved this viewpoint [5]. Recent and earlier cross-sectional studies also suggested that *H. pylori* infection had protective effects on asthma [6–9]. However, not all studies supported this result, which still requires future research [10–16]. Although the effects of *H. pylori* in the pathophysiological mechanisms of asthma still remain controversial, the researchers detected *H. pylori* exotoxin VacA in human lung biopsies and directly stimulated pulmonary airway epithelial cells to secrete inflammatory cytokines in vitro [17]. Moreover, *H. pylori* has been discovered in the lung tissues of patients with COPD [18]. More studies confirmed that existence of *H. pylori* provided protective effects against asthma, and eradication of *H. pylori* may have a negative impact [19–21].

The immune system includes adaptive immunity (acquired immunity) and innate immunity (natural immunity) [22–24]. Adaptive immunity mainly recognizes “non-self” antigen and produces immune tolerance, and innate immunity is the first line of defense against pathogenic microorganism invasion, which can effectively distinguish self from pathogenic microorganism [25, 26]. The immune pathogenesis of allergic asthma is quite complex. The studies have focused on Toll-like receptors (TLRs), dendritic cells (DCs), helper T cells 1/2 (Th1/Th2), Th17, regulatory T cells (Tregs), etc. The formation of a complex interaction network between cells and receptors also provides a broad view for immunological research of asthma [27–29]. The followings are the possible protective mechanisms of *H. pylori* against allergic asthma reported in recent years and the possible associated treatment of asthma.

### Possible Protective Mechanisms of *H. pylori* against Allergic Asthma

#### The Hygiene Hypothesis

The hygiene hypothesis [30, 31] links early environmental and microbial exposure to the prevalence of atopic allergies and asthma. The exposure to environment and microbes can help to form the growing immunity system and protect subsequent immune-mediated diseases [32]. “Unhygienic exposure” to microorganisms in an early age can prevent the development of allergic diseases in later years [33]. *H. pylori* infection usually occurs in children, and the way to be infected is related to unhygienic family environment or habits, and this association appears in mouse asthma models [34]. Early studies [35] have shown that the hygiene hypothesis may be related to Th1/Th2 imbalance. Synthetic adjuvants or microbial components can directly influence the cells in the innate immune system, including NK and DCs cells, and also stimulate the secretion of interferon-γ (IFN-γ), IL-12, and IFN-α, leading to the phenotypic transformation of allergen-specific Th2 to Th1 cells [7, 36]. The specific mechanisms still need to be further studied.

#### Adjusting Th1/Th2 Balance

It has been proved that Th1/Th2 ratio imbalance is one of the essential immunological mechanisms of asthma. According to the responses to foreign antigens, T cells can be divided into 2 types of effector cells, Th1 and Th2, which have totally different functions [37, 38]. Th1 mainly secretes IL-12, IFN-γ, and transforming growth factor β (TNF-β), activates macrophages and causes cytotoxicity, and mediates cellular immunity. Th2 mainly secretes IL-4, IL-5, and IL-13, activates B cells to produce immunoglobulin, and mediates humoral immunity. Th1 and Th2 are restrictive to each other and reach a balance. Asthma is a disease characterized by the count of Th2 and the effects it exerts [39–41].

*H. pylori* neutrophil-activating protein (HP-NAP) is one of the main virulence factors of *H. pylori*, which is also applied as a possible biomarker in the diagnosis of *H. pylori*-related diseases [42]. Studies [43–45] have shown that HP-NAP plays a protective role in asthma, which
could stimulate Th1 activation and attenuate Th2 response in allergy-related asthma both in vitro and in vivo (Fig. 1). In the research by Karakullukcu et al. [46], 18 cases (20.4%) of *H. pylori* DNA were discovered in 88 healthy stool samples but none in 92 asthmatic children (3–8 years). Multivariate Logistic regression analysis suggested that HP-NAP had a protective effect on asthma in male children. In order to verify HP-NAP as a regulatory factor against the Th2 inflammatory effect, Zhou et al. [47] exposed the mice to purified recombinant *H. pylori* NAP (rNAP) through intraperitoneal injection or inhalation. The increase and infiltration of the eosinophils were remarkably suppressed in the lungs of the asthma mice model induced by ovalbumin (OVA). Moreover, the count of eosinophils was decreased in the lavage fluid from bronchoalveolar (BALF) in the mice treated with rNAP. Additionally, the levels of IL-13 and IL-4 declined \((p < 0.01)\), the levels of IFN-\(\gamma\) and IL-10 elevated \((p < 0.01)\), and the serum level of IgE declined \((p < 0.01)\) in experimental groups in comparison with the control group. It is suggested that mucosal and systemic pretreatment of rNAP might attenuate asthma in the mice induced by OVA. Furthermore, rNAP could be used as a new method in preventing or treating allergic disorders.

**Adjusting Thl7/Tregs Balance**

With the development of scientific research, Thl/Th2 imbalance cannot fully explain the mechanisms of asthma [49]. Although allergic asthma is often associated with abnormal TH2 cellular responses, a group of patients with severe disease showed a mixture of TH2 and TH17 cellular responses in the airways [50]. It was found that Th7 and Tregs cells were also significantly related to the pathogenesis of asthma [51–53]. Synergy of multiple pathways, such as Th2, Th17, and even eosinophil/neutrophil infiltration, has been found in some asthma models [54–56]. The view that eosinophilic asthma is an exclusive TH2 disorder and neutrophil asthma is an exclusive TH17 disorder may be oversimplified [57]. It has been found that the TH2 and TH17 inflammatory pathways regulate each other in asthma [58]. Th1/Th2 and Th7/Tregs and their various cytokines form an extremely complex interactive network [59, 60]. Th7 cells are defined as “proinflammatory” immune cells, which mainly secrete IL-17, mediate inflammatory responses, and pro-

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**Fig. 1.** *H. pylori* promotes Th1 activation and inhibits Th2 response through HP-NAP in allergic asthma. HP, *H. pylori*; HP-NAP, *H. pylori* neutrophil-activating protein; Th0/Th1/Th2, helper T cells 0/1/2.
mote neutrophil maturation, proliferation, and chemotaxis. Retinoid-related orphan receptor (ROR) gamma t (RORγt) is a key transcriptional factor in the differentiation of Th17 cells. The deletion of RORγt leads to the failure of Th17 differentiation [61, 62]. Tregs secrete IL-10 and other inhibitory cytokines. Tregs play an important role in maintaining immune balance. Tregs specifically express forkhead transcription factor p3 (Foxp3), suppress immune response, and mediate immune tolerance [63–65].

The protective mechanisms of \textit{H. pylori} in inflammatory diseases such as asthma may be associated with induction of Tregs, which could highly suppress the immune activity [66–68]. Published data strongly suggested that \textit{H. pylori} caused an increase in the response levels of Tregs, Th1, and Th17 in mouse models and human, which could prevent asthma. According to the ontogeny of the immune system, \textit{H. pylori} tends to infect in one’s childhood and continues to stimulate immunity reaction throughout the life, including Th1, Th17, and Tregs responses. Additionally, children infected by \textit{H. pylori} tend to have a stronger Tregs response than adults [69–72]. Once human is infected by \textit{H. pylori}, Tregs are found to be highly active in the gastric mucosa. The secretion of IL-10 by Tregs in peripheral blood was significantly higher than that in \textit{H pylori}-specific Th1 cells. When there was a strong Tregs reaction, the concentration of total IgE and allergen-specific IgE was low. Suppressing IL-10 could significantly restore the IgE reaction in animal models. Therefore, systematic IL-10 and Tregs may play a role in preventing allergies mediated by \textit{H. pylori} [72].

Kyburz et al. [73] established C57BL/6 mice experimental models of house dust mite- or ovalbumin-induced airway inflammation and influenza A virus or \textit{Citrobacter rodentium} infection. It was found that the exposure to \textit{H. pylori} extract or its immunomodulator vacuolating cytotoxin in the perinatal stage could exert robust protective functions against allergic inflammation in the airway not only in the offspring of the first generation but also the second generation, which did not increase the susceptibility to bacterial or viral infection. The immune responses correlated with prevention of allergy include inhibiting the activities of effectors or T cells, expanding the subsets of regulatory T cells expressing RORγt, and FOXP3 demethylation. The diversity and composition of the microbiota in the gastrointestinal system are notably influenced by the perinatal exposure of \textit{H. pylori}. In conclusion, \textit{H. pylori} exposure not only works on the carriers but also on the next generations. Maternal nutrient, the exposure to microorganisms, tobacco, and other environmental factors influence the formation of the immune system in a fetus via an epigenetic way (Fig. 2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2}
\caption{\textit{H. pylori} has a protective effect on asthma by inducing highly immunosuppressive Tregs and inhibiting Th17. HP, \textit{H. pylori}; Tregs, regulatory T cells; RORγt, retinoid-related orphan receptor (ROR) gamma t; Foxp3, forkhead transcription factor p3.}
\end{figure}

\textbf{Inhibition of DCs}

DCs can devour and kill invasive microorganisms and present microbial antigens to T cells, thus participating in the innate immunity [25, 74]. DCs help the initial T cells polarize into Th2 effector cells or differentiate into Tregs [75, 76]. It has been suggested that \textit{H. pylori} targets DCs to promote immune tolerance and enhance the protective effect against allergic asthma, and this effect relies on highly suppressed Tregs [77, 78]. Oertli et al. [79, 80] found the level of Foxp3, the main regulatory factor expressed by Tregs, was increased in immature T cells when \textit{H. pylori} was exposed to DCs in cells and animal experiments. Depleting the DCs in \textit{H. pylori}-infected mice in the neonatal stage resulted in the improvement of infection control and the destruction of specific tolerance to \textit{H.
Helicobacter pylori. At the same time, it also aggravated the immune-pathological reactions driven by T cells. IL-18 secreted by DCs could directly act on T cells and promote transformation into Tregs. It promotes specific immune tolerance and asthma protection in mice. Vacuolating cytotoxin A (VacA) and γ-glutamyl transpeptidase (GGT), 2 virulence factors in H. pylori, independently interfere with the maturation of DCs, thus promoting the tolerance of DCs. Shiu et al. [81] found that the infection of H. pylori can upregulate the expression of anti-inflammation factors including IL-1 receptor-associated kinase M (IRAK-M). The expression of IRAK-M activated by TLRs in DCs directly inhibited the inherent function of DCs, such as the upregulation of cytokines and costimulatory molecules, rather than affecting the response of Th17 and Tregs (Fig. 3).

**Activation of TLRs**

TLRs are a group of widely studied pattern recognition receptors, which are associated with the incidence and progression of asthma. At present, it is considered that TLRs are mainly expressed in the membrane or organelle capsule of antigen presenting cells (such as macrophages and DCs). TLRs participate in the early host defense and play an important role in the innate immune response. On the other hand, TLRs participate in the inflammatory response via secreting cytokines, chemokines, adhesion molecules, etc., and finally activate the acquired immune system. Different TLRs have different functions [82–84]. TLR2 is an important pattern recognition receptor in Tregs [85, 86] and TLR9 mainly plays a negative role in the regulation of allergic inflammation [87–89]. TLR4 not only relies on conserved sequences encoded by embryological genes to identify pathogenic microorganisms and activate innate immunity but also regulates adaptive immunity [90, 91]. In conclusion, TLRs are closely related to asthma [92].

In recent days, hypotheses were proposed that H. pylori could facilitate the activation of inflammasomes in mouse and human immune cells. The possible mechanisms and virulence factors stimulating the inflammasome have been discovered in animal and cell models. IL-1β could facilitate the responses of Th1 and Th17. IL-18 has been a hallmark in humans and mice infected by H. pylori, which plays an important role in H. pylori persistence, Tregs differentiation, and prevention of asthma. The secretion of IL-1β induced by H. pylori is regulated by the activation of NLRP3 (Nod-like receptor family member), caspase-1, and TLR2. The axis of TLR2/NLRP3/caspase-1/IL-18 was essential in the regulation of H. pylori-specific immune response which could prevent inflammatory bowel disease and asthma induced by allergens in mouse models [93–95].

NOD1 is considered as a pattern recognition receptor in cells and specifically targets the Gram-negative peptidoglycan, which plays an important role in host defense against infections (e.g., H. pylori and Shigella flexneri) [96]. The variations in the NOD1 gene contribute to inflammatory bowel disease and asthma. NOD1 could be activated by a rather low concentration of M-Tri DAP, which is a specific muropeptide ligand. Moreover, NOD1 could induce minimal secretion of IL-10, TNF-α, and IL-1β from...
Peripheral blood mononuclear cells in human and synergistically facilitated the responses induced by TLRs. Synergistic responses occurred across a variety of cytokine secretions (GM-CSF, IL-10, IL-4, IL-6, IL-1β, IL-1α, and TNF-α) and various ligands (to TLR5, 7/8, 2/6, 1/2, 4) [97].

TLR9 could partly contribute to the initiation of immunity responses induced by bacteria via binding to the unmethylated CpG-DNA rich in bacteria. A well-reported single nucleotide polymorphism (SNP) in the TLR9 promoter (TLR9-1237T/C) is related to multiple inflammatory diseases, such as atopy, allergic asthma, and inflammatory bowel disease. The sequence of the TLR9 promoter gene was analyzed, and the results demonstrated that carrying the variant “C” allele on position −1237 formed a possible site to bind NF-κB, which could theoretically stimulate the transcriptional process of the gene [98]. It has also been shown that the type IV secretion system of H. pylori facilitated the synthesis of IL-8 through the p38 protein kinase (p38MAPK) pathway in the primary tracheobronchial epithelial cells collected from young rhesus monkeys. It was suggested that the innate immune response in airway epithelial cells in infants infected by H. pylori was enhanced, but the TLR4 pathway was not essential in this process [99].

Reduction of Gastroesophageal Reflux

Gastroesophageal reflux can induce or aggravate asthma. Several possible mechanisms have been raised. The first is stimulation theory. The airway is stimulated by the aspiration resulting from the reflux, which increases airway responsiveness. The second is reflex theory. Since esophagus and bronchus are derived from the same embryonic organ, the autonomic innervation is similar. Reflux not only stimulates esophagus but also activates the vagus nerve, thus inducing bronchospasm and aggravating asthma [100, 101]. It has been shown that H. pylori inflammation changed gastric hormonal status and influenced the autonomic nervous system. H. pylori can also reduce gastroesophageal reflux [102].

The Gut-Lung Axis Theory

In recent decades, the role of gut flora in the pathogenesis of asthma has been extensively studied [103–105]. The gut and lungs interact with each other through microbes and immune functions, achieve bidirectional regulation, and amplify immune signals. It is known as the gut-lung axis [106]. Gut and lung microbes have certain homology at early colonization. They all first pass through the oropharynx and then enter the digestive tract or respiratory tract through swallowing or breathing [107].

Microorganisms in the gastrointestinal tract can reach the lower respiratory tract through gastroesophageal reflux [108]. Due to the increase of intestinal and alveolar capillary permeability in some patients, the bacteria from the intestinal mucosa can be transferred to the lungs through the blood circulation [109]. Changes in the pulmonary flora can also cause changes in the intestinal flora through the blood flow [110]. However, there is little evidence about direct shift of microorganisms between 2 sites [107].

Disorders of the gut can be observed in lung diseases [105, 111–114]. Influenza virus can change the composition of intestinal flora and cause intestinal immune damage through Th17 cell mediation [115]. Locally induced pulmonary anaphylaxis may also affect the composition of intestinal flora [116]. Studies have shown that the severity of intestinal symptoms is highly consistent with the severity of pulmonary symptoms [117, 118].

Intestinal microbes promote development of the body’s immune system early in life and affect the whole body and lungs through the blood and lymphatic system [104]. Both the gut and lungs have a strong mucosal defense system. For instance, intestinal and respiratory mucosal goblet cells can secrete IgA. The intestinal microflora can regulate pulmonary immune responses through bacterial lipopolysaccharide, short-chain fatty acids (SCFAs), and immune cells (e.g., Tregs and DCs), which can affect colonization of the lung microbiome [106, 119, 120]. The imbalance of intestinal flora is related to a variety of lung diseases such as asthma. The adjustment of intestinal flora can alleviate the symptoms and reduce the incidence of asthma. Probiotics supplementation has a certain preventive and therapeutic effect on asthma in mice. High-fiber diet can change the intestinal flora of mice and increase the content of SCFAs, thus inhibiting the activity of Th2 cells [121]. H. pylori can cause chronic immunopathologic changes in the stomach and dysbacteriosis and promote regulation of the immune function of the lung. H. pylori protects asthma by DCs, Tregs, etc., which is consistent with the gut-lung axis theory [106, 110, 122] (Fig. 4).

Reducing the Expression of Heat Shock Protein 70

Heat shock protein 70 (HSP70), an ATP-dependent chaperone protein, is a known inhibitor of caspase activation, showing antiapoptotic activity in a variety of cells [123, 124]. It has been found that HSP70 might play a role in promoting asthma inflammation. HSP70 deficiency leads to significant reduction in airway inflammation, goblet cell proliferation, and Th2 cytokine production, including IL-4, IL-5, and IL-13, and targeting HSP70 can
alleviate the potential utility of allergen-induced Th2 cytokines, goblet cell proliferation, and airway inflammation [125–127]. HSP70/CD80 DNA vaccine can inhibit airway remodeling by regulating the development of Th1/Th2 subsets in asthma mice, and HSP70 may be a potential target for inhaled glucocorticoids (ICS) in the treatment of asthma [128, 129]. Another study also found that HSP70 directly inhibited irritation-induced gastric ulcer formation and promoted gastric ulcer healing [130]. HSP70 can also protect the gastric mucosa through inhibition of apoptosis, proinflammatory cytokines, and cell adhesion molecules [131, 132]. *H. pylori* infection alters gastric epithelial cell proliferation and reduces or even abolishes HSP70 gene expression [133, 134]. The possible mechanisms included inducing the cellular protective effect of HSP70 against *H. pylori* infection via inhibiting the expression of inducible nitric oxide synthase (iNOS). However, the reliability and accuracy, as well as the underlying mechanisms, in this relationship remains poorly understood, and large-sample clinical research must be performed to verify this theory [135, 136]. The direct mechanism of HSP70 related *H. pylori* in protecting asthma remains to be further explored.

**The “Disappearing Microbiota” Hypothesis**

*H. pylori* is a kind of ancient, dominant bacteria that settle in the human stomach and closely attach to host cells. *H. pylori* might be a regular member in the gastric microflora in human. With the improvement of environment and lifestyle, and the eradication of *H pylori*, the prevalence of *H. pylori* infection in the developed countries has declined sharply, while the incidence of asthma, obesity, and allergic diseases has increased rapidly [137–139]. According to Blazer [140], the proponent of the “disappearing microbiota” hypothesis, the absence of certain bacterial species from the ancestral microbiota could
change the environment where cognitive, metabolic, and immunological functions develop in our early life. This change could result in the increased susceptibility to some diseases. The disappearance of ancient microbiota may be a universal paradigm leading to modern diseases. This harmful trend implies that we need to put efforts in understanding and reversing the reasons contributing to the disappearing microbiota [5].

**Treatment of Asthma Related to H. pylori Infection**

Eradicating *H. pylori* could decrease the occurrence of dyspepsia, peptic ulcer, and gastric malignancy. However, concerns of extensive application of eradication treatment are also raised, such as the resistance to antimicrobial agents and an increase in the prevalence of disorders that are negatively correlated with the infection of *H. pylori*, including obesity, asthma, GERD, and Barrett esophagus [141, 142]. Eradicating the infection of *H. pylori* is considered as a double-edged sword. Thus, selective identification and elimination of only the virulent strains of *H. pylori* are of great importance in the eradication therapy [143]. Epidemiology studies and experiments have demonstrated that exposure to *H. pylori* could prevent asthma, especially in one’s childhood. Recently, in vivo studies have shown that live bacteria are not involved in induction of this protective role. Administering an extract of *H. pylori* in a newborn could prevent inflammation in the airway and metaplasia of the goblet cells. Injection of *H. pylori* extract could inhibit DCs in processing the allergen in the mediastinal lymph nodes and lungs. These results suggest that the extract of *H. pylori* following sensitization could effectively prevent allergic airway disorders [144]. *H. pylori* targets DCs and relies on highly suppressed Tregs. Since HP-NAP is considered as a possible regulator for Tregs and can inhibit allergic inflammation of asthma [78, 145, 146], van Wijck et al. [147] have shown that *H. pylori* extract can effectively reduce the production of mucus and multiple characteristics of inflammation in the mice rechallenged by house dust mite. VacA and GGT, 2 persistence determinants in *H. pylori*, are sufficient in preventing asthma and could be given in their purified forms for treatment [148]. Transmaternal *H. pylori* exposure can reduce allergic airway inflammation in the offspring through Tregs and also provide new insights for interventional therapy of asthma [73]. High doses of vitamin D and fish oil supplements during pregnancy have been shown to help prevent and control disease in the offspring [149], and maternal treatment of Zika virus infection with the IL-1 receptor antagonist can directly reduce fetal neuroinflammatory response through placental immunity [150]. Immunological methods can be used to design vaccines against *H. pylori* infection, and it should also be used for the prevention of asthma across generations [64, 68, 70]. VacA, GGT, HP-NAP, Tregs, and even FOXP3 each play an important role in *H. pylori*-related asthma protection. It would be a very interesting topic if we could design an effective monoeptope or multieptope vaccine that could be used by the mother before pregnancy, during pregnancy, or during breastfeeding to prevent asthma of the offspring through the placenta or breast milk.

**Conclusion**

*H. pylori* may protect allergic asthma by regulating Th1/Th2 and Thl7/Tregs balance, inhibiting DCs and HSP70, activating TLRs, and reducing gastroesophageal reflux. The hygiene hypothesis, the “disappearing microbiota” hypothesis, and the gut-lung axis theory all support this protective effect. Therapeutic products made by *H. pylori* may be used to prevent and treat asthma. In particular, perinatal exposure to *H. pylori* can reduce allergic airway inflammation in the offspring, which also provide a new insight for interventional treatment of asthma.

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**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Z.Z. and F.Y. conceived and designed this study and contributed equally to this work. Y.M., Y.S., C.B., and C.L. participated actively in the study and approved the submitted manuscript.
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