

# Research on the Mechanism and Application of Acupuncture Therapy for Asthma: A Review

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**Abstract:** Asthma is a high-risk disease based on airway hyperresponsiveness (AHR). In this review, we found that there are many studies on clinical therapy for asthma that focus on the efficacy of acupuncture therapy and its mechanisms, including the functional connectivity of different brain regions, with the aid of functional magnetic resonance imaging (fMRI), immune responses/cell recognition (innate lymphoid cells and balance of Th1/Th2 and Treg/Th17), intracellular mechanism (autophagy, endoplasmic reticulum stress, and epigenetic alteration), and ligand–receptor/chemical signaling pathway (neurotransmitter, hormone, and small molecules). In this review, we summarized the clinical and experimental evidence for the mechanisms of acupuncture therapy in asthma to offer insights into drug discovery and clinical therapy. Given the paucity of clinical studies on the mechanisms of acupuncture in the treatment of asthma, this review notably included studies based on animal models to investigate the mechanisms of acupuncture in the treatment of asthma.

**Keywords:** asthma, acupuncture therapy, acupoint, mechanism, fMRI

## Introduction

Asthma is a common chronic disease that affects children and adults, with approximately 300 million people affected worldwide.<sup>1</sup> The prevalence of asthma in the Americas is much lower than that in Africa and accounts for about 10% of global prevalence, including 25 million people with asthma in the United States, 6.4 million of whom are children.<sup>2</sup> According to the Centers for Disease Control Home Interview data, the percentage of adults with asthma was 8.7% in 2022, which was an increase from 8% in 2019.<sup>3</sup> Asthma is an immune disease that involves a complicated immunoreaction. Recent studies on asthma endotypes have defined two types, namely, type 2 inflammation (T2)-high, and T2-low (non-type 2) asthma.<sup>4</sup> Type 2 is induced by pathogens, while non-type 2 asthma is induced by a number of factors, such as cigarette smoke, obesity, and PM2.5. Although various drugs are applied for the clinical treatment of asthma, inhaled corticosteroids are still in the first line. However, long-term use of inhaled corticosteroids not only causes immunity system dysfunction<sup>5</sup> but may even induce epigenetic alteration of the offspring, including higher levels of cortisol and glucocorticoid receptors (GR).<sup>6</sup> Clinical studies have shown that acupuncture significantly reduces the side effects of corticosteroids,<sup>6,7</sup> and acupuncture therapy might be a hope for patients with glucocorticoid resistance.

Acupuncture, a part of traditional Chinese medicine (TCM), is an effective medical therapy that has been used in the treatment of various diseases during the last 2000 years. According to the World Health Organization (WHO), 43 diseases are effectively treated by acupuncture, and bronchitis, bronchial asthma, pneumonia, bronchiectasis, and pulmonary emphysema are common respiratory system diseases effectively improved by acupuncture therapy. The effects of acupuncture therapy are not yet well understood because the mechanism of action is not sufficiently known. Response to the stimulation of acupoints is associated with the dysfunction of certain organs in a way that the stimulation of appropriate acupoints could adjust the function of the dysfunctional organs. For example, issues with brain function could be improved by adjusting the gut,<sup>8</sup> or asthma with lung dysfunction could be cured by stimulating effective acupoints at the back region or lower limbs.<sup>9,10</sup> However, the mechanisms of acupuncture therapy in asthma remain a

puzzle. Many studies have focused on the mechanism of acupuncture and tried to explain it with the use of advanced technologies, such as magnetic resonance imaging (MRI), electroencephalography, and magnetoencephalography.<sup>11</sup> These technologies have revealed that acupuncture can induce body responses by stimulating specific acupoints. In the early stage of acupuncture research, functional magnetic resonance imaging (fMRI) was used to observe the effects of stimulation based on blood-oxygen-level-dependent contrast, and the results confirmed that stimulation of certain acupoints could modulate the activity of autonomic nervous system, hypothalamus, dorsal raphe nucleus, periaqueductal gray (PAG), and rostroventral medulla.<sup>12</sup> To identify the effector substances of acupuncture therapy, research focusing on the key substances has shown an increase in the level of substance P (SP) upon stimulating Feishu (BL13), Dingchuan (EX-B1), and Huagai (CV20).<sup>13</sup> Clinical practice has offered abundant evidence that stimulating acupoints could clearly reduce cytokine levels and affect the balance of Th1/Th2 and Treg/Th17 in asthma.<sup>14,15</sup>

We found that studies on the use of acupuncture therapy in treating asthma have focused on functional connectivity (FC) in fMRI data, immunity, intracellular mechanism, and ligand-receptor signaling, while only a few studies focused on neuroscience. To further promote the research and application of acupuncture, this review focuses on the treatment of asthma with acupuncture from the perspective of molecular biological mechanisms, including some of the neuromodulation of acupuncture for asthma (Figure 1).

### Pathology of Asthma

Chronic inflammation as a remarkable characteristic of asthma is reflected in all patients with asthma. Namely, inflammatory cell (eg, mast cells, eosinophils, macrophages, lymphocytes, neutrophils) infiltration, mucosal edema, increased permeability of blood vessels, bronchial smooth muscle spasm, ciliated epithelial cell detachment, goblet cell proliferation, and increased secretion in the respiratory tract are noteworthy and characteristic pathological signs of asthma.<sup>16</sup> With recurrent attacks of asthma, airway remodeling takes place.<sup>17</sup> The aforementioned pathological signs

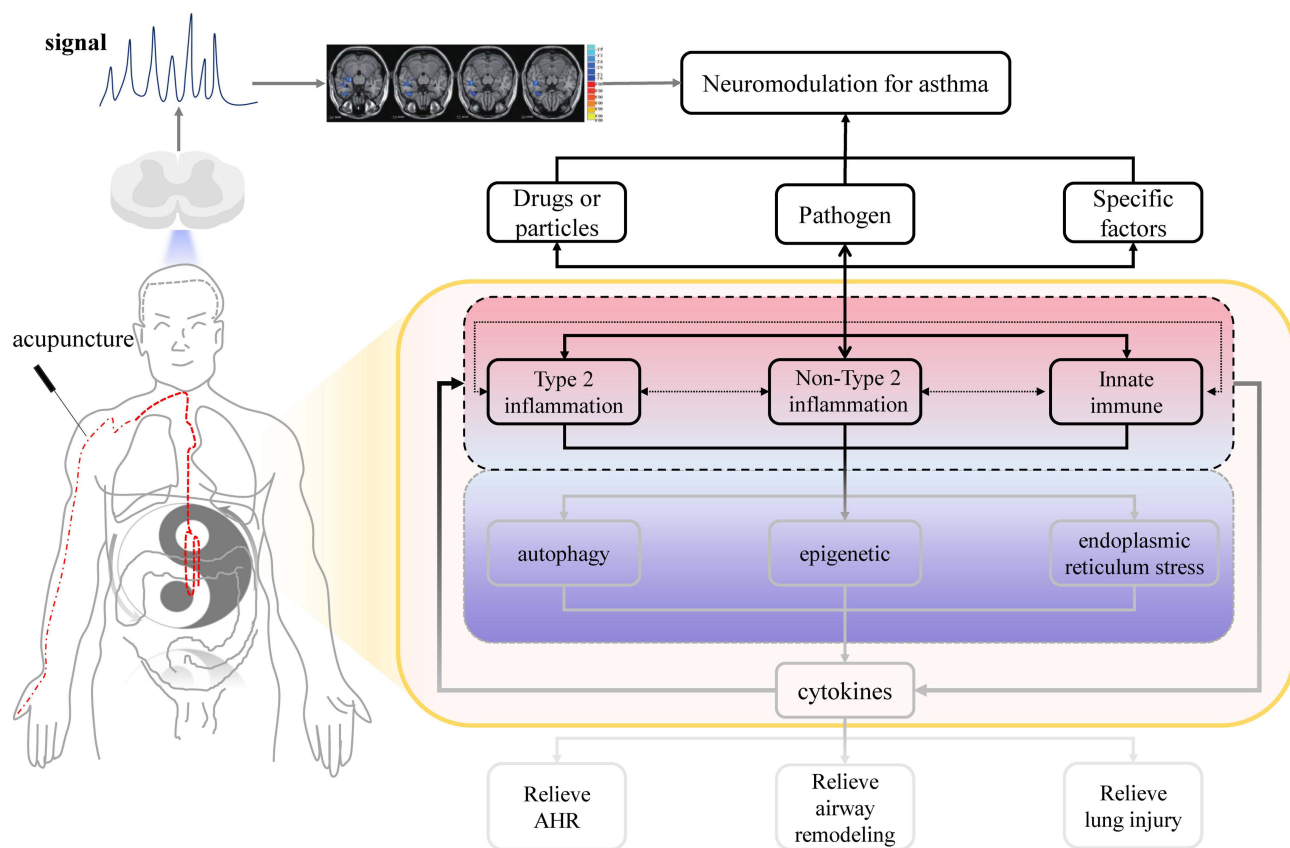


Figure 1 The mechanisms of acupuncture therapy in treating asthma.

cannot meet the needs of clinical diagnosis of asthma, and researchers tend to apply molecular diagnosis to accurately classify asthma into clinical syndromes.

At present, most studies explain the pathogenesis of asthma by inflammatory responses. Asthma is usually classified into two types, namely, type 2 inflammation and non-type 2, according to inflammatory responses in the clinic. Balancing the inflammatory responses of cells such as Th1/Th2, Treg/Th17, and pulmonary group 2 innate lymphoid cells (ILC2s); inhibiting cytokines; and blocking IgE have become focuses during the treatment of asthma.<sup>18</sup>

## Acupoints for Asthma

Acupuncture is gradually accepted by patients because its effects develop rapidly. TCM has treated asthma for thousands of years, and the ancients summarized effective acupoints for clinical practice, especially in children with asthma.<sup>19</sup> Clinical research has shown that certain acupoints are more sensitive in patients with asthma. These acupoints are distributed on the bladder meridian, lung meridian, and large-intestine meridian; they include acupoints such as Feishu (BL13), Xinshu (BL15), Chize (LU5), and Jueyinshu (BL14); and anatomical position of these sensitive points is related to nerve segments C4, C6, and T1–T6.<sup>20,21</sup> According to clinical reports, the effective acupoints are Dazhui (GV14), Danzhong (CV17), Feishu (BL13), Zhongfu (LU1), Zusanli (ST36), Dingchuan (EX-B1), Sanyinjiao (SP6), and Fengmen (BL12).<sup>22</sup> These acupoints are mainly located on the lung meridian, conception vessel, stomach meridian, and bladder meridian, and these points are in agreement with a meta-analysis and data from Chinese clinical practice.<sup>23–25</sup> Apart from the common acupoints mentioned above, other auxiliary points are also essential to relieve the syndrome of asthma, for example, Yuji (LU10), Lieque (LU7), Fenglong (ST40), and Fuliu (KI7). The acupoints are mainly distributed in the back region and limbs of the body (Table 1, Figure 2).

**Table 1** Information Associated with Key Acupoints

No.	Criticality	Standard Name*	Acupoints	Meridian	Location**	Application Principles <sup>▲</sup>
1	Main acupoints	BL13	Feishu	Bladder meridian	On the upper back region, at the same level as the inferior border of the spinous process of the third thoracic vertebra (T3), 1.5 B-cun lateral to the posterior median line	Asthma; cough
2		LU1	Zhongfu	Lung meridian	On the anterior thoracic region, at the same level as the first intercostal space, lateral to the infraclavicular fossa, 6 B-cun lateral to the anterior median line	Asthma; cough
3		CV22	Tiantu	Conception vessel	In the anterior region of the neck, in the center of the suprasternal fossa, on the anterior median line	Asthma; cough
4		CV17	Danzhong	Conception vessel	In the anterior thoracic region, at the same level as the fourth intercostal space, on the anterior median line	Asthma; cough; oppression in the chest
5		LU6	Kongzui	Lung meridian	On the anterolateral aspect of the forearm, on the line connecting LU5 with LU9, 7 B-cun superior to the palmar wrist crease	Asthma; cough
6		EX-B1	Dingchuan	Extra points	In the back region, at the same level as the inferior border of the spinous process of the seventh cervical vertebra (C7), 0.5 B-cun lateral to the posterior median line	Asthma; cough
7		ST40	Fenglong	Stomach meridian	On the anterolateral aspect of the leg, lateral border of the tibialis anterior muscle, 8 B-cun superior to the prominence of the lateral malleolus	Asthma; cough; phlegm
8	Auxiliary acupoints	BL12	Fengmen	Bladder meridian	In the upper back region, at the same level as the inferior border of the spinous process of the second thoracic vertebra (T2), 1.5 B-cun lateral to the posterior median line	Cough; fever; pulmonary heat

(Continued)

Table 1 (Continued).

No.	Criticality	Standard Name*	Acupoints	Meridian	Location**	Application Principles <sup>▲</sup>
9		BL11	Dazhu	Bladder meridian	In the upper back region, at the same level as the inferior border of the spinous process of the first thoracic vertebra (T1), 1.5 B-cun lateral to the posterior median line	Cough; fever
10		GV14	Dazhui	Governor vessel	In the posterior region of the neck, in the depression inferior to the spinous process of the seventh cervical vertebra (C7), on the posterior median line	Cough; asthma; heat symptom complex
11		LI11	Quchi	Large intestine meridian	On the lateral aspect of the elbow, at the midpoint of the line connecting LU5 with the lateral epicondyle of the humerus	Obstruction syndrome
12		SP3	Taibai	Spleen meridian	On the medial aspect of the foot, in the depression proximal to the first metatarsophalangeal joint, at the border between the red and white flesh	Splenic asthenia
13		BL20	Pishu	Bladder meridian	In the upper back region, at the same level as the inferior border of the spinous process of the 11th thoracic vertebra (T11), 1.5 B-cun lateral to the posterior median line	Edema; abdominal distension; diarrhea
14		ST36	Zusanli	Stomach meridian	On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 B-cun inferior to ST35	Asthma; cough; edema; yang deficiency syndrome
15		BL23	Shenshu	Bladder meridian	In the lumbar region, at the same level as the inferior border of the spinous process of the second lumbar vertebra (L2), 1.5 B-cun lateral to the posterior median line	Asthma; dysuria; edema
16		CV4	Guanyuan	Conception vessel	On the lower abdomen, 3 B-cun inferior to the center of the umbilicus, on the anterior median line	Yang deficiency (impotence, dysuria, diarrhea, etc.)
17		KI3	Taixi	Kidney meridian	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon	Cough; asthma; deficiency of both qi and yin
18		BL15	Xinshu	Bladder meridian	In the upper back region, at the same level as the inferior border of the spinous process of the fifth thoracic vertebra (T5), 1.5 B-cun lateral to the posterior median line	Cough; cardiodynia
19		CV6	Qihai	Conception vessel	On the lower abdomen, 1.5 B-cun inferior to the center of the umbilicus, on the anterior median line	Yang deficiency (impotence, dysuria, diarrhea, etc.)
20		PC6	Neiguan	Pericardium meridian	On the anterior aspect of the forearm, between the tendons of the palmaris longus and the flexor carpi radialis muscles, 2 B-cun proximal to the palmar wrist crease	Cardiodynia; vomit
21		HT6	Yinxi	Heart meridian	On the anteromedial aspect of the forearm, radial to the flexor carpi ulnaris tendon, 0.5 B-cun proximal to the palmar wrist crease	Asthma; yin deficiency syndrome

(Continued)

Table 1 (Continued).

No.	Criticality	Standard Name*	Acupoints	Meridian	Location**	Application Principles <sup>▲</sup>
22		KI7	Fuliu	Kidney meridian	On the posteromedial aspect of the leg, anterior to the calcaneal tendon, 2 B-cun superior to the prominence of the medial malleolus	Edema; deficiency of kidney yin
23		SP6	Sanyinjiao	Spleen meridian	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus	Deficiency syndrome
24		LU7	Lieque	Lung meridian	On the radial aspect of the forearm, between the tendons of the abductor pollicis longus and the extensor pollicis brevis muscles, in the groove for the abductor pollicis longus tendon, 1.5 B-cun superior to the palmar wrist crease	Cough; asthma
25		LI4	Hegu	Large intestine meridian	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone	Pain induced by heat symptom complex
26		LU10	Yuji	Lung meridian	On the palm, radial to the midpoint of the first metacarpal bone, at the border between the red and white flesh	Cough; asthma; fever
27		LU5	Chize	Lung meridian	On the anterior aspect of the elbow, at the cubital crease, in the depression lateral to the biceps brachii tendon	Cough; asthma
28		BL17	Geshu	Bladder meridian	In the upper back region, at the same level as the inferior border of the spinous process of the seventh thoracic vertebra (T7), 1.5 B-cun lateral to the posterior median line	Cough; asthma
29		LU9	Taiyuan	Lung meridian	On the anterolateral aspect of the wrist, between the radial styloid process and the scaphoid bone, in the depression ulnar to the abductor pollicis longus tendon	Asthenia of both lung and kidney; asthma

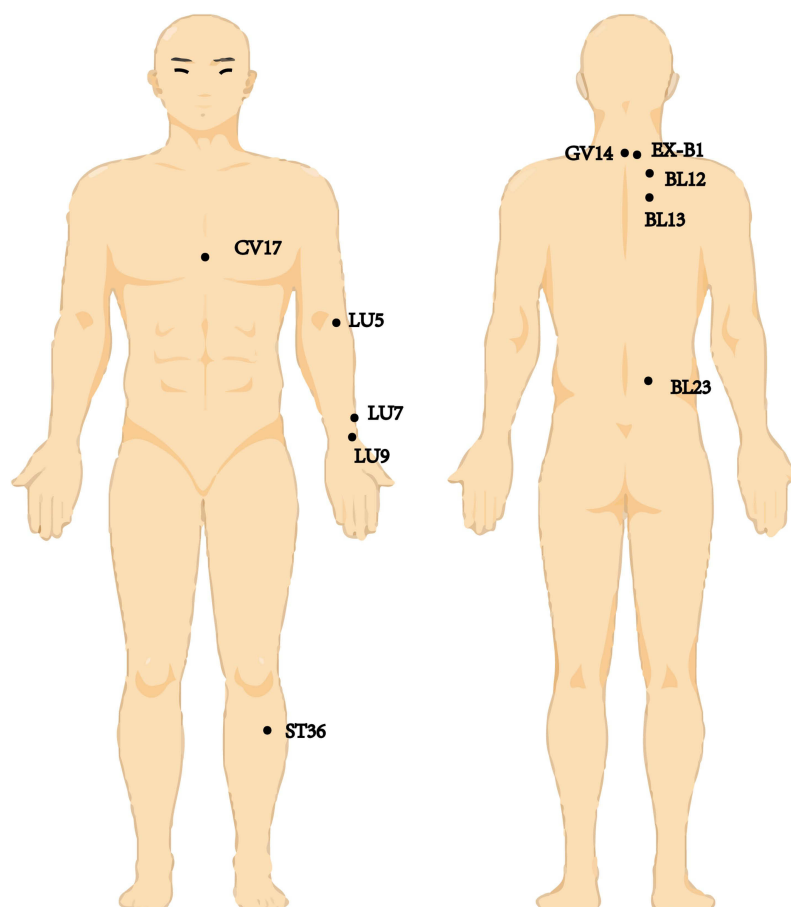
**Notes:** \*Standard name, also known as WHO standard acupuncture point, collected from the book "WHO standard acupuncture point locations in the western pacific region". \*\*Locations, collected from the book "WHO standard acupuncture point locations in the western pacific region". <sup>▲</sup>Application principles, collected from old Chinese medical books and clinical reports.

## Authenticated and Reasonable Mechanism of Acupuncture

Based on the retrieved data, the mechanism of acupuncture for treating asthma mainly involves the following two categories: neuromodulation based on fMRI, and molecular mechanism (cell recognition/inflammatory responses, intracellular mechanism, and ligand–receptors/chemical signaling pathway) based on molecular biology.

### Neuromodulation for Asthma

The link between the brain and asthma was first demonstrated in 2005, when researchers used fMRI to identify six patients with antigen-induced mild asthma and followed them for 4 weeks, collecting fMRI, blood, and lung function data at various times after the intervention stimulus; they found that the anterior cingulate cortex (ACC) and the insula were significantly activated.<sup>26</sup> In 2012, the research team further increased the sample size and showed that there was a dual response to antigenic stimulation: a bronchoconstrictor response phase and an inflammatory response phase.<sup>27</sup> The results of Rosenkranz et al showed that in patients with high-stress asthma, the hypothalamus–pituitary–adrenal (HPA) axis responded more strongly when acute stress occurred, and that activity in the anterior insula of the brain was enhanced during acute stress, reflecting the role of stress in modulating inflammation. The enhanced activity of the mid-insula and ACC was associated with an increased expression of airway inflammation and proinflammatory cytokines.<sup>28</sup> Wang et al showed that the lingual gyrus and the calcarine sulcus, representing the visual network, had significantly higher dynamic voxel-voxel-mirror homomorphic connectivity (dVMHC) in patients with asthma than in healthy



**Figure 2** Common acupuncture points and their locations.

subjects. The asthma group had significantly lower dVMHC than the control group in the medial superior frontal gyrus, anterior/middle/posterior cingulate gyrus, and sensorimotor network supplementary motor area.<sup>29</sup>

Asthma is characterized by dyspnea and reduced lung ventilation, and dyspnea and pain sensation involve similar brain regions, mainly including the insula, dorsal ACC, amygdala, and medial thalamus. Experimental studies on dyspnea in healthy subjects have shown that dyspnea could activate the insular cortex.<sup>30</sup> Other MRI measures showed no significant differences in insula ReHo values between healthy subjects and patients with asthma. However, an FC study showed that the FC of the left ventral anterior insula (vAI) and postcentral gyrus, bilateral occipital lobe, and left precentral gyrus was attenuated in patients with asthma compared with healthy subjects, whereas the mean FC values of the left vAI and right middle temporal gyrus, left cerebellum posterior lobe, and bilateral ACC were enhanced, which could be used to effectively discriminate patients with asthma from healthy subjects. In addition, the enhanced mean FC values in the right vAI and left putamen and right caudate nucleus could well discriminate between healthy subjects and patients with asthma.<sup>31</sup>

The results of an fMRI-based asthma study showed that needling Dazhui (GV14), Fengmen (BL12), and Feishu (BL13) resulted in decreased FC of the vAI with the left pallidum and increased FC of the right dorsal anterior insula (dAI) with the right precentral gyrus, right angular gyrus, and right supra-frontal gyrus in the asthmatic group. In the asthmatic group, the FC of the right posterior insula (PI), right inferior temporal gyrus, and right superior temporal gyrus was weakened at baseline compared with that of the healthy group. After acupuncture, a significant difference between the vAI and the whole brain disappeared, and the FC between the right dAI and the left anterior central gyrus, left posterior cingulate gyrus, left angular gyrus, and right anterior cuneus enhanced. The FC between the right dAI and the left and right posterior central gyrus, right anterior central gyrus, and left posterior cingulate gyrus was enhanced. This



result suggests that acupuncture enhanced the FC between subregions of the right insula and the brain regions associated with the default mode network in patients with asthma.<sup>32</sup> In their follow-up study, Chen et al validated this result and also found that the FC between the left insula and the bilateral posterior central gyrus, precentral gyrus, posterior cingulate gyrus, and precuneus was weakened in patients with asthma after acupuncture.<sup>33</sup>

In addition to the abovementioned results regarding brain functional connections, the transmission of nerve signals is also the most direct and effective evidence of the benefits of acupuncture in the treatment of asthma. As mediators of nerve signal transmission, neurotransmitters (including acetylcholine (ACh) and SP) should not be ignored in acupuncture intervention in asthma. ACh is distributed in the neuromuscular junctions, parasympathetic nerves, and preganglionic fibers of sympathetic nerves. The stimulus from acupuncture can be projected to the vagus nerve nucleus through the center, activate efferent vagus nerve fibers, promote the release of ACh from peripheral nerve endings and its binding to  $\alpha 7nAChR$  on immune cells; inhibit the release of pro-inflammatory factors through intracellular signaling pathways, and regulate inflammation.<sup>34</sup> Tracey's team found that ACh inhibits the release of pro-inflammatory mediators during inflammatory responses in vivo or in vitro. In addition, between the nervous system and the immune system, there is an anti-inflammatory pathway mainly composed of the vagus nerve and ACh: the cholinergic anti-inflammatory pathway. This pathway plays a role in regulating the systemic and local inflammatory response.<sup>35,36</sup> Others have also demonstrated that acupuncture regulates the electrical activity of nucleus tractus solitarii, afferent nerve fibers, and efferent nerve fibers to control heart rate, blood pressure, and gastrointestinal motility.<sup>37–39</sup>

## Cell Recognition

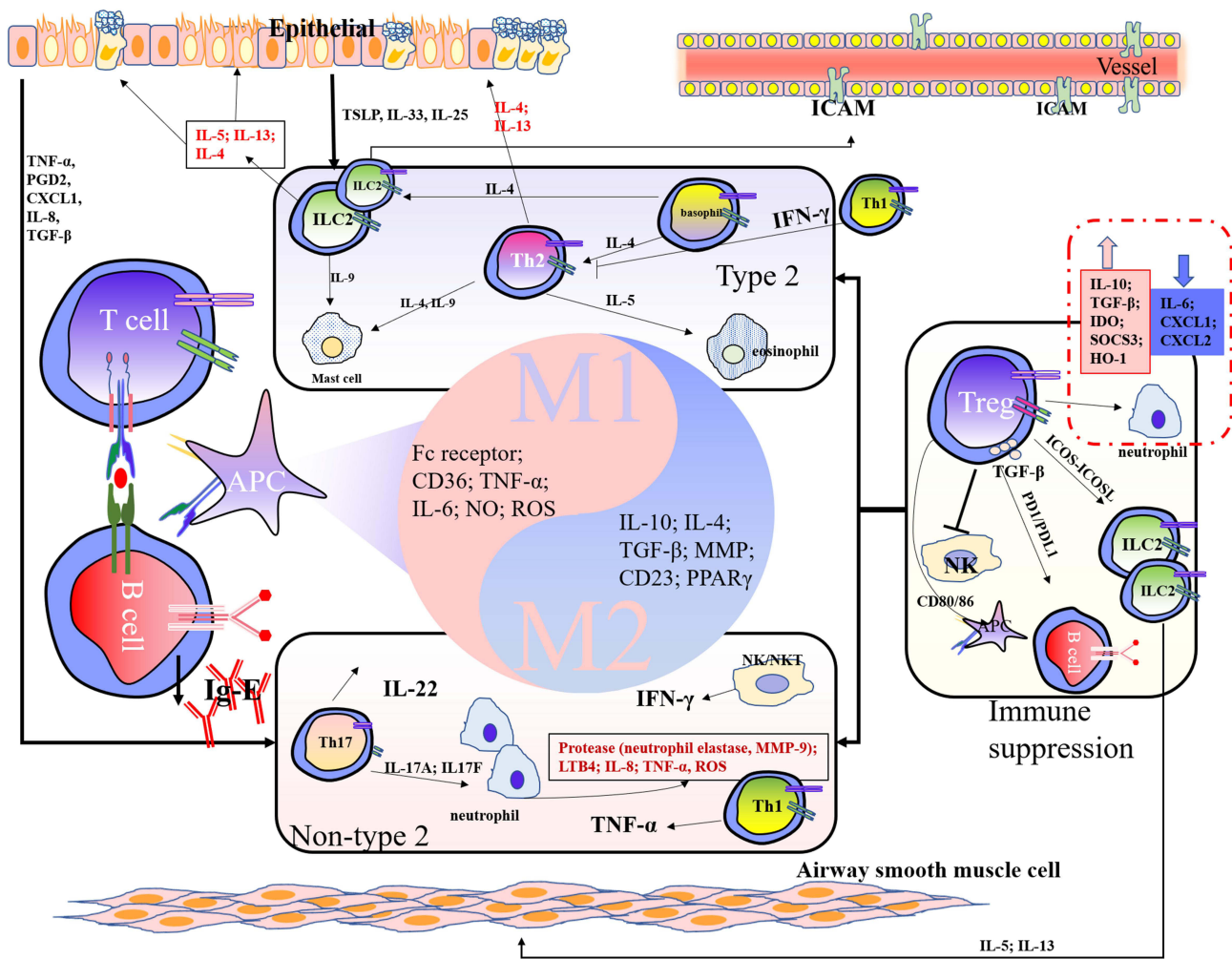
Cell recognition dependent on cytokines is a key point in the pathogenesis of asthma and also plays an important role in immunity.<sup>40</sup> According to the retrieved data of acupuncture therapy, current studies focusing on the relationship between asthma and immunity are divided into those focusing on pulmonary group 2 innate lymphoid cells (ILC2s) and those on balancing Th1/Th2 and Treg/Th17 (Figure 3). Researchers have adopted flow cytometry to observe the number of multiple inflammatory cells, and the results indicated that the regulation of inflammatory cells could be regarded as a breakthrough for acupuncture therapy in treating asthma.

### Pulmonary Group 2 Innate Lymphoid Cells

ILC2s mainly play a crucial role in type 2 inflammation. When allergic asthma starts, epithelial barrier is damaged, and epithelial cells secrete cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. IL-25 and IL-33 can directly induce ILC2 cell activation and release IL-4, IL-5, IL-9, and IL-13, related to differentiation and proliferation of immune cells. Epithelial-derived TSLP regulates reactive oxygen species (ROS) production and mitophagy through AMPK activation and histone modification and alters M1/M2 chemokine CCL1 expression in human monocytes.<sup>41</sup> TSLP, IL-9, IL-4, and IL-13 also act on airway epithelial cells, impairing the epithelial further, and impair airway smooth muscle cells (ASMCs), inducing their migration and proliferation.<sup>41,42</sup> Acupuncture at GV14, Feishu BL13, and BL12 reduces IL-4, IL-5, IL-9, and IL-13 in bronchoalveolar lavage fluid (BALF) and serum,<sup>43,44</sup> and certain chemokines that control differentiation and polarization of immune cells (such as CCL1, CCL5, and CCL11) are also reduced in serum.<sup>45,46</sup> An imbalance of cytokines breaks the vessel barrier by inducing the expression of key adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1) or intercellular adhesion molecule 1 (ICAM-1).<sup>16</sup> An asthma rat model intervened by acupuncture at BL13, CV17, and EX-B1 showed that MAPK and ICAM-1 were reduced in the lung tissue, suggesting that acupuncture therapy could also protect the vessel barrier and further relieve airway remodeling.<sup>47</sup> Clinical research has shown that high circulating concentration of IL-6 is associated with more severe asthma. IL-6 is regulated by IL-1 $\beta$ , so high levels of IL-6 and IL-1 $\beta$  appear at the same time.<sup>16</sup> Clinical acupuncture therapy at BL13 in children with asthma could significantly reduce IL-6 and IL-1 $\beta$  in serum<sup>48</sup> and relieve the forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) induced by asthma.<sup>49</sup>

### Balance of Th1/Th2 and Treg/Th17

Th1/Th2 balance is a clinical marker of type 2 inflammation, and drug discovery also focuses on the inhibition of inflammatory responses and cytokines. Cytokine detection in BALF, serum, and lung tissue decreases after acupuncture



**Figure 3** Inflammation and cell recognition in asthma.

for asthma. Acupuncture therapy in treating asthma involves the stimulation of certain acupoints to enhance Th1 cell responses or inhibit Th2 responses based on IFN- $\gamma$  secreted from Th1. An asthma model showed that stimulation at GV14, BL13, and BL12 could increase IFN- $\gamma$  in the BALF and lung tissue.<sup>44</sup> GV14, BL13, and ST36 are another acupuncture formula and could reduce cytokines related to Th2, such as IL-4 and IL-5, through elevating the level of T-bet, thereby controlling the differentiation of Th1 and inhibiting cytokine synthesis in Th2.<sup>50,51</sup>

Treg/Th17 balance as a marker of non-type 2 inflammation, and severe asthma often exists in specific groups, such as obesity, cancer, and even in glucocorticoid resistance. Clinical reports have revealed that upregulated level of Treg cells can block type 2 inflammation and non-type 2 inflammation based on cell recognition in asthma, such as the connection between ICOS/ICOSL, PD1/PDL1, and CD80/CD86. Acupuncture at GV14, BL13, and BL12 could reduce CD4<sup>+</sup>IL-17A<sup>+</sup> cells and increase CD4<sup>+</sup>Foxp3<sup>+</sup> cells in BALF, thereby recovering the balance between Th17 and Treg.<sup>52,53</sup> Another study focused on the relationship between ST36 and Treg cells and found that only the stimulation at ST36 enhanced the number of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells.<sup>15</sup>

Dendritic cells and macrophages have high differentiation capacity and can differentiate to different subtypes through various cytokines stimulation. Dendritic cells and macrophages are divided at least into subtype 1 and subtype 2, and they maintain balance in Th1/Th2 and Treg/Th17 through the transformation of subtypes.<sup>4</sup> Although this transformation of subtypes has not yet attracted more attention, acupuncture therapy in treating asthma involves multiple cytokines and transcription factors related to the transformation of subtypes of dendritic cells and macrophages, which indicates that the



transformation of subtypes of dendritic cells and macrophages related to asthma is involved in the balance of inflammatory responses.<sup>4,54</sup>

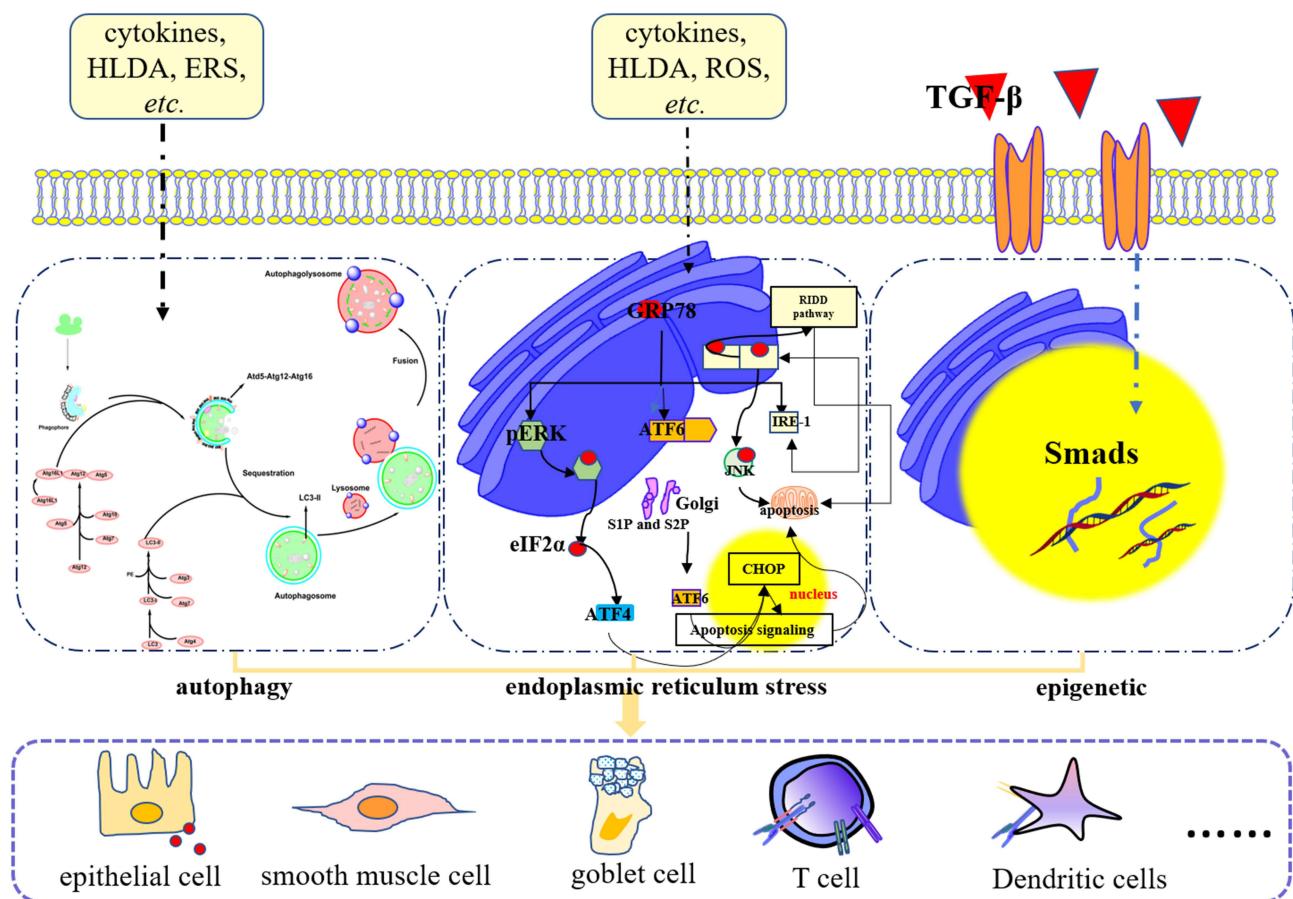
## Intracellular Mechanism

Autophagy, endoplasmic reticulum stress, and epigenetic alterations are active topics in the field of acupuncture therapy for asthma (Figure 4). Autophagy and endoplasmic reticulum stress play crucial roles in the activation and regulation of inflammasomes,<sup>55</sup> anti-infection,<sup>56</sup> balancing inflammation in innate immunity, and inflammatory cell development and maturation.<sup>57,58</sup> Epigenetic alteration is another crucial mechanism of asthma therapy, and it is related to the heritability of asthma and determines the quality of life of offspring.<sup>59</sup>

## Endoplasmic Reticulum Stress

Endoplasmic reticulum stress (ERS) is an important factor in airway remodeling and inflammatory responses. Unfold protein response is a trigger of ERS. Three pathways involved in ERS are the pERK signaling pathway, IRE1 signaling pathway, and ATF signaling pathway, and drug discovery based on ERS revealed that blocking ERS had an effect on asthma treatment.<sup>60</sup> Studies focusing on AHR have found that ERS causes injury of epithelial cells, smooth muscle cells, and goblet cells. ERS is involved in the inflammatory responses mediated by cytokines, such as IL-13, TNF- $\alpha$ , IL-4, and IL-5, which regulate ERS through negative feedback and exacerbate asthma by enhancing ERS.<sup>61</sup>

Proline-rich extensin-like receptor kinase/eukaryotic translation initiation factor 2A (PERK/eIF2), endoplasmic reticulum-to-nucleus signaling 1/x-box-binding protein 1 (IRE1 $\alpha$ /XBP1), and activating transcription factor 6 alpha/endoplasmic reticulum resident protein 57 (ATF6 $\alpha$ /ERp57)—all markers of ERS—have been detected in smooth muscle cells and epithelial cells in the lungs in asthma.<sup>62–64</sup> Acupuncture at GV14, BL13, and ST36 significantly downregulates



**Figure 4** Intracellular mechanism involved in asthma.

the expression of p-PERK, p-IRE-1, 78-kDa glucose-regulated protein (Grp78), and ATF6 to suppress ERS and relieve asthma by inhibiting ERS.<sup>51</sup> Besides, ERS can induce autophagy in target cells, and autophagy might enhance airway remodeling (Balance of Th1/Th2 and Treg/Th17).

### Autophagy

Single-nucleotide polymorphism analysis has revealed that the genes associated with autophagy are mutated and involved in asthma.<sup>65,66</sup> Recent studies have revealed that some cytokines, such as IL-17, IL-13, IL-4, IL-1 $\beta$ , and vascular endothelial growth factor A (VEGFA), regulate autophagy and affect airway remodeling and loss of lung function in asthma,<sup>67–70</sup> even self-autophagy of immune cells.<sup>71</sup> Depletion of the autophagy-related gene ATG5/ATG14 in human tracheobronchial epithelial cells can inhibit MUC5AC (mucin 5AC, oligomeric mucus/gel forming) secretion, so airway remodeling induced by IL-13 is relieved.<sup>72</sup> Similarly, an autophagy-related gene ATG5-depleted A549 cells and human small primary airway epithelial cells induced by IL-1 $\beta$  also revealed that blocking the level of autophagy could suppress cytokine secretion.<sup>69</sup> In terms of T-lymphocyte differentiation, the genes related to autophagy regulate CD4-cell differentiation and are involved in the balance of Th1/Th2 and Th17/Treg.<sup>51</sup> In addition to the regulation of the above target cells, autophagy also sustains B-cell survival induced by IL-4 to exacerbate allergic asthma through the JAK signaling pathway via an mTOR-independent, class III phosphatidylinositol 3-kinase (PtdIns3K)-dependent pathway.<sup>65</sup>

GV14, BL12, and BL13 are effective acupoints and have been verified in long-term clinical practice.<sup>71</sup> Animal models have also revealed that stimulation of GV14, BL12, and BL13 can decrease various cytokines<sup>53,73</sup> (Table 2), and studies on animal models of asthma have indicated that the efficacy of acupuncture for asthma stems from the inhibition of multiple cytokines (eg, IL-4, IL-17) of airway smooth muscle cells and inflammatory cells to relieve symptoms of asthma and airway remodeling by downregulating the level of autophagy-related proteins (ATG5, Beclin-1, p62, and LC3B) in lung tissue.<sup>51</sup>

**Table 2** Formula and Mechanism of Acupuncture Therapy for Asthma in the Last 10 Years

NO	Reference	Model	Acupoints	Acupuncture Parameters	Mechanism	Effects
1	Yu, 2023 <sup>74</sup>	Rat	GV14; BL12; BL13	Once every other day	Reduce p-p38MAPK	Inhibit proliferation of ASMC
2	Tang, 2023 <sup>75</sup>	Mouse	GV14, BL12, BL13	Once a day for 3 days	Reduce IL-4, IL-13, MDA, oxidized GSH, and the non-heme Fe <sup>2+</sup> level; downregulate the expression of ACSL4-15-LO1	Alleviate RL; relieve erastin-induced exacerbation of lung inflammation and lipid peroxidation in ferroptosis
3	Tang, 2022 <sup>76</sup>	Rat	BL13; EX-B1; CV17	Catgut-embedding once	Reduce p38MAPK, ICAM-1, and IL-4	Inflammatory cells are absent from blood vessels; eosinophils are decreasing
4	Teng, 2021 <sup>77</sup>	Mouse	GV14; BL12; BL13	Catgut-embedding once	Decrease IL-4, IL-13, and IgE in the BALF <sup>#</sup> ; downregulate the expression of p-NF- $\kappa$ B p65 and IFN- $\gamma$ increase	The percentage of R <sub>L</sub> increases slower; the percentage of Cdyn decreases slower; the proliferation of ILC2s, leukocytes, eosinophils, lymphocytes, and neutrophils is inhibited
5	Yang, 2021 <sup>78</sup>	Human	EX-B1; BL13; ST36; CV17	Catgut-embedding semimonthly	Decrease IgA and IgE in the serum	PEF, FEV1, MEF25%, MEF50%, MEF75%, and MEF25%–75% are higher than in the control group
6	Wang, 2022 <sup>79</sup>	Human	LU9; LU7; LU5	Three times per week for 4 weeks	N/A	The scores of FEV1, PEF, Asthma control test, and Asthma Quality of Life Questionnaire increase

(Continued)

Table 2 (Continued).

NO	Reference	Model	Acupoints	Acupuncture Parameters	Mechanism	Effects
7	Zhao, 2021 <sup>51</sup>	Mouse	GV14; BL13; ST36	Every other day for 13 days	Downregulate the expression of proteins and mRNAs related to autophagy (ATG5, Beclin-1, p62, and LC3B) and endoplasmic reticulum stress (p-PERK, p-IRE-1, Grp78, and ATF6); increase in IFN- $\gamma$ and decrease in IL-4, IL-17, and TGF- $\beta$ in the BALF, lung tissue, and serum	Inflammatory cells decrease; suppressed level of autophagy and endoplasmic reticulum stress; balance of Th1/Th2 and Treg/Th17; R <sub>L</sub> decrease
8	Qiao, 2021 <sup>80</sup>	Mouse	BL13; LU1	Once daily for 2 weeks	Reduce IgE and IL-4 and increase IFN- $\gamma$ ; upregulate the expression of PI3K, Foxp3, and ROR $\gamma$ 1	Suppress inflammatory responses
9	Zheng, 2021 <sup>81</sup>	Rat	GV14; BL12; BL13	Once a day for 7 days	Downregulate the expression of Bcl-2 and upregulate the expression of Fas	Reduce eosinophils and enhance apoptosis of eosinophils
10	Tang, 2021 <sup>45</sup>	Mouse	GV14; BL12; BL13	Retained for 20 min	Reduce IgE, CCL5, CCL11, and IL-17A in BALF and IL-4, IL-5, and IL-13 in serum; downregulate the expression of SLC3A2 and ATPIA3; enhance the level of SOD and GSH, and lower the level of MDA	Relieve R <sub>L</sub> and enhance Cdyn; decrease the inflammatory score, PAS+ epithelial cells, and eosinophils
11	Hu, 2020 <sup>46</sup>	Rat	GV14; BL12; BL13	Once a day for 7 days	Downregulate the expression of CCL1, CCR8, and STAT6	Reduce inflammatory responses
12	Cheng, 2021 <sup>82</sup>	Human	I. LU9; LU7; LU5; HT3; HT6; HT7	Retained for 30 min	N/A	FEV1, PEF, The Self-rating Anxiety Scale, and Self-rating Depression Scale are improved
13	Yu, 2020 <sup>83</sup>	Human	I. LU9; LU7; LU5; HT3; HT6; HT7	Three times a week	N/A	Improve the Asthma Control Test (ACT), the peak expiratory flow rate (PEFR), and forced expiratory volume in 1 s (FEV1)
14	He, 2021 <sup>84</sup>	Rat	GV14; BL12; BL13	Once a day for 7 times	Downregulate the expression of FIZZ1, NOTCH1, and $\alpha$ -SMA	Inhibit the differentiation of fibroblasts, reduce the proliferation of smooth muscle
15	Cui, 2021 <sup>43</sup>	Mouse	GV14; BL12; BL13	Every other day for 2 weeks	Reduce IL-5, IL-9, IL-13, IL-25, IL-33, and soluble IL-33 receptor (sST2)	Relieve R <sub>L</sub> and enhance Cdyn; decrease the inflammatory score, PAS+ epithelial cells, and eosinophils; inhibit the proliferation of ILC2s
16	Zhou, 2020 <sup>85</sup>	Rat	GV14; BL12; BL13	Every other day for 13 days	Upregulate the expression of MT-2, Akt1, and CaMK2 $\beta$ ; induced phosphorylation of 14 proteins is upregulated, while that of 37 proteins is downregulated	Relieve R <sub>L</sub>
17	Hua, 2020 <sup>50</sup>	Rat	GV14; ST36; BL13	Retained for 20 min	Downregulate IL-5 and GATA-3 and upregulate IFN- $\gamma$ and T-bet	Balance Th1/Th2; suppress inflammation responses
18	Chen, 2020 <sup>86</sup>	Rat	GV14; BL12; BL13	30 min a day on every other day	Increase cAMP/cGMP and substance P; downregulate vasoactive intestinal peptide, neurokinin A, and neurokinin B	Alleviate neurogenic inflammation and hyperresponsiveness of the airway

(Continued)

Table 2 (Continued).

NO	Reference	Model	Acupoints	Acupuncture Parameters	Mechanism	Effects
19	S. Elsheikh, 2019 <sup>87</sup>	Human	LU5; LU7; LU9; SP6; ST36; BL13; BL23; CV17; GV14	N/A	N/A	Relieve R <sub>L</sub>
20	Dong, 2019 <sup>52</sup>	Mouse	GV14; BL12; BL13	Every other day for 4 weeks	Upregulate T-bet, FOXP3+, and IL-10, and reduce IL-5, IL-13, IL-17A, and RAR-related orphan receptor gamma t (RORγt)	Upregulate the cell numbers of CD4 + interferon gamma (IFN-γ)+, CD4+ Foxp3+, and CD4+ IL-17A+; balance CD4+ T cell subtypes
21	Nurwati, 2019 <sup>88</sup>	Mouse	BL13; ST36	Three times a week for 6 weeks	N/A	Reduce neutrophils, eosinophils, and goblet cells; reduce thickness of the bronchioles
22	Liu, 2018 <sup>89</sup>	Mouse	GV14; BL13; ST36	Once a day for three days	Reduce TGF-β1 in BALF and downregulate the expression of Smads, type-I, and α-SMA	Relieve R <sub>L</sub>
23	Dong, 2018 <sup>90</sup>	Mouse	GV14; BL12; BL13	Every other day for 2 weeks	Reduce TNF-α, IL-1β, and IL-33; increase sST2	Relieve R <sub>L</sub> and enhance Cdyn; reduce the inflammatory responses, PAS+ epithelial cells, and CD4 +IL-17A+ (Th17) cells;
24	Han, 2018 <sup>91</sup>	Human	LU6; EX-B1; BL13; LU10	Retained for 20 min	Reduce NGF and MMP-9	Upregulate Th1/Th17; relieve FEV1, PEF, FEV1/FEV
25	Chen, 2017 <sup>92</sup>	Rat	BL13; BL23	Retained for 30 min, once daily for 14 days	Reduce IL-1β and IgE	Reduce CD8+ T cells; relieve inflammatory responses
26	Yang, 2017 <sup>93,94</sup>	Rat	GV14; BL13; BL12	Once every two days, for seven times	Downregulate the expression of Akt and p-Akt	Relieve inflammatory responses
27	Xu, 2017 <sup>95</sup>	Rat	GV14; BL13; BL12	Acupuncture for 15 min or 30 min	N/A	Inhibit ACh-induced contractile responses of airway smooth muscle cells (ASMCS)
28	Yang, 2017 <sup>96</sup>	Rat	GV14; BL13; BL12	Retained for 20 min, once other day	Downregulate the expression of PI3K	Relieve R <sub>L</sub> and Cdyn
29	A. Dabbous, 2017 <sup>19</sup>	Human	CV17; LU5; LU7; LU9; ST36; SP6; GV14; BL13; BL23; LI4	Laser acupuncture for 2 min per point; three sessions per week	N/A	Relieve FEV1 and FVC
30	Wei, 2017 <sup>97</sup>	Mouse	GV14; BL13; BL12	Every other day for 4 weeks	Reduce TNF-α, IL-1β, IL-5, and eotaxin; increase CORT and ACTH	Relieve R <sub>L</sub> and inflammatory cells, enhance Cdyn
31	Wang, 2016 <sup>98</sup>	Rat	GV14; BL13; BL12	Retained for 20 min	Increase CORT	Relieve R <sub>L</sub> and eosinophils
32	Yu, 2016 <sup>99,100</sup>	Rat	GV14; BL13; BL12	Once other day for 14 days	Reduce TGF-β, c-fos; downregulate p-p38MAPK	Reduce leukocytes and eosinophils; relieve R <sub>L</sub>
33	Dong, 2015 <sup>73</sup>	Mouse	GV14, BL12, BL13, BL23	Three times a week for 6 weeks	Reduce IL-17A, IL-4, and IL-5 in BALF and serum; increase IFN-γ and IL-10	Relieve R <sub>L</sub> and enhance Cdyn; lower inflammatory score

(Continued)

Table 2 (Continued).

NO	Reference	Model	Acupoints	Acupuncture Parameters	Mechanism	Effects
34	Wei, 2015 <sup>53</sup>	Mouse	GV14; BL13; BL12	Every other day for 4 weeks	Reduce IL-17A, IL-17F, IL-22, and IgE; suppress the expression of IL-17R, ROR $\gamma$ t, p65, and NF- $\kappa$ B kinase- $\alpha$ (IKK $\alpha$ )	Relieve R <sub>L</sub> and enhance Cdyn; reduce leukocytes, eosinophils, neutrophils, and CD4+IL-17A+ cell numbers, and increase CD4+Foxp3+ cell numbers in BALF
35	Ke, 2015 <sup>101</sup>	Human	BL13; CV17; LI4; GV14; ST40; LU1; LU6	Once a day for three days	Reduce C-RP, Ig E, IL-1, IL-6, and TNF- $\alpha$ in the serum	Relieve the syndrome of asthma
36	Li, 2014 <sup>102</sup>	Rat	GV14; BL13; BL12	Once a day for 10 days	Reduce TGF- $\beta$ in the lung	Decrease the thickness of the airway wall and smooth muscle
37	Tang, 2014 <sup>103</sup>	Mouse	GV14; BL13; BL12; EX-B1; BL23; BL20	Once a day for 7 days	Reduce thymic stromal lymphopoietin (TSLP) and GATA; increase T-bet	Decrease the thickness of the airway wall and smooth muscle
38	Ngai, 2013/2011 <sup>104,105</sup>	Human	BL13/LU7; LU9	N/A	N/A	Decrease the skin impedance and heart rate variability (LF/HF)/increase the skin impedance at LU7 and LU9
39	Fu, 2014/2013; Zhu, 2013; Tan, 2012 <sup>10,106–108</sup>	Human	LU1, LU5, LU7; LI11, LI4, ST25; LU5, LU7, LI4, ST25	Every other day, three times a week for 12 weeks	N/A	Improve PEF, FEV1, MEF25%, MEF50%, and MEF75%
40	Wang, 2014 <sup>109</sup>	Rat	GV14; BL13; BL12	Once every two days, for seven times	Reduce p38MAPK	Reduce eosinophils
41	Yang, 2013 <sup>71</sup>	Human	GV14; BL13; BL12	Once every other day for 5 weeks	Reduce secretory IgA (sIgA) and total IgA in the saliva and IgE in the serum	Reduce CD3+, CD4+, CD8+, IL-2R+ T lymphocytes, and eosinophils
42	Cui/ Yang 2013 <sup>110,111</sup>	Rat	GV14; BL13; BL12	Once a day for 7 days	Reduce pan-Ras and c-fos/ reduce c-fos and p38MAPK	Relieve the syndrome of asthma
43	Yin, 2010/2009 <sup>112,113</sup>	Rat	GV14; BL13; BL12	Five consecutive days	Reduce Dusp1, S100A9, and MT-2	Relieve the syndrome of asthma
44	Chen, 2012 <sup>114</sup>	Rat	BL13, BL23, CV17; BL23; BL13, CV17	Catgut-embedding once	N/A	Relieve inflammatory responses
45	Wang, 2012 <sup>115</sup>	Rat	GV14; BL13; BL12	Once two days for seven times	Reduce Cav3.3	Relieve inflammatory responses
46	E.R. Carneiro, 2010 <sup>116</sup>	Rat	GV14, BL13, EX-B1, LU1, CV17, ST36, SP6	Every other day for 2 weeks	Increase IL-1, IFN- $\gamma$ , and IL-4; reduce NO, IL-10, and LTB4	Balance Th1/Th2
47	Yan, 2010 <sup>117</sup>	Rat	GV14; BL13; BL12	Once two days for seven times	Increase surfactant protein-A in BALF	Relieve the syndrome of asthma

**Abbreviations:** #BALF, bronchoalveolar lavage fluid; RL, airway resistance; Cdyn, lung dynamic compliance.

## Epigenetic Alterations

According to a longitudinal study of 21,541 twins based on a bivariate genetic model to estimate the importance of genetic and environmental factors in the heritability of asthma, the contribution of genetics was estimated at 0.917 and the genetic analysis showed the heritability of 80% at the ages of 3 and 7 years.<sup>118</sup> Epigenetic research has also revealed

that DNA methylation of the genes associated with asthma offers evidence for the heritability of asthma, and the results are consistent with the clinical tests that cover many genes, such as NOTCH-1, GR, ILs, CCLs, and GATA3.<sup>6,59,119</sup> Genetic experiments have demonstrated that acupuncture for asthma, especially stimulation of ST36, can improve the epigenetics of offspring.<sup>6,119,120</sup>

ST36 is one of the most important auxiliary acupoints for relieving symptoms of asthma and reversing lung damage, and its stimulation has shown clinical efficacy. Experimental studies have demonstrated that the stimulation of ST36 significantly relieves lung resistance and enhances dynamic compliance, increases the alveolar number, and decreases the mean linear intercept and septal thickness.<sup>6,119</sup> In addition, stimulation of ST36 reduces cortisol and downregulates the expression of GR, which markedly improves corticosteroid resistance that results from corticosteroid abuse and decreases the inflammatory responses of offspring by upregulation of the PPAR $\gamma$  signaling pathway<sup>6,7,119</sup> and inhibition of TGF- $\beta$ /Smads/HDAC involved in the acetylation of NF-kappa B.<sup>89,121</sup> These data indicate that acupuncture could change the genetic characteristics of the offspring.

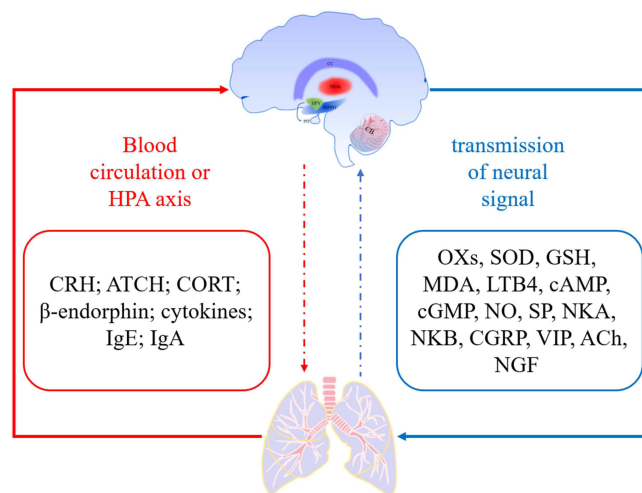
## Ligand–Receptor/Chemical Signaling Pathway

Ligand–receptor signaling is the main form of life activities and is regarded as a direct communication mode among neurons and in cell–cell interaction. According to the data collected, neurotransmitters, small molecules, and steroids are involved in the occurrence and development of asthma (Figure 5).

### Neurotransmitters

In contrast to inflammatory factors, the association of neurotransmitters with asthma is insufficiently clear. In fact, pulmonary neuroendocrine cells are spread over the bronchia of patients with asthma and show certain relevance for asthma.<sup>122</sup> Recent studies related to acupuncture therapy for asthma have demonstrated that some neurotransmitters, such as SP, neurokinin A (NKA), neurokinin B (NKB), calcitonin-gene related peptide (CGRP), vasoactive intestinal peptide (VIP), acetylcholine (ACh), and nerve growth factor (NGF), are involved in the pathology of asthma. SP, NKA, NKB, and CGRP are involved in contraction of airway smooth muscle (ASM);<sup>123</sup> ACh induces bronchoconstriction by mediating the physiological actions of the parasympathetic system; and VIP induces bronchodilation. Besides, the neurotransmitters even participate in lung resistance and airway remodeling by mediating inflammatory cytokines.<sup>122</sup>

GV14 and BL13 are common acupoints in acupuncture therapy for asthma. Experiments have revealed that the stimulation of GV14 relieved neurogenic inflammation in asthma rats by reducing CGRP, NGF, NKA, NKB, and SP.<sup>124</sup> Stimulation of BL13 has been shown to repair muscarinic acetylcholine receptor M2 and downregulate the expression of muscarinic acetylcholine receptor M1, muscarinic acetylcholine receptor M3, acetylcholinesterase, and choline acetyltransferase in the lung to inhibit ACh release.<sup>125</sup> The formula of acupuncture also shows better efficacy than individual



**Figure 5** Ligand–receptor chemical signaling pathway involved in asthma.



acupuncture points in clinical practice. Stimulation of acupoints GV14, BL12, and BL13—a common acupuncture formula—has been shown to reduce VIP, NKA, NKB, and SP in the lung to alleviate neurogenic inflammation and hyperresponsiveness of the airway.<sup>86</sup> Orexins (OXs) are neuropeptides secreted from the hypothalamus and are involved in the respiratory system. Reducing OX and downregulating the expression of OX receptors by stimulating BL13 and ST36 could relieve FEV<sub>0.1</sub>/FVC and FEV<sub>0.3</sub>/FEV and decrease the alveolar septum thickening and edema with inflammatory cell infiltration by downregulating inflammatory cytokines.<sup>88,126</sup>

### Small Molecules

Small molecules, such as superoxide dismutase (SOD), glutathione (GSH), (MDA) malonaldehyde, leukotriene B4 (LTB4), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and nitric oxide (NO), are also related to asthma and are involved in oxidative stress injury of airway, apoptosis of bronchial cells, and signal transmission.<sup>127</sup> Oxidative stress injury is an accompanying mechanism and influences the recovery of injury induced by asthma. Experimental studies have selected SOD, GSH, and MDA as markers to evaluate the recovery of lung after oxidative stress injury<sup>45,75</sup> and regarded cAMP/cGMP as a signal to evaluate the balance of second messengers involved in inflammatory cells and bronchial smooth muscle dysfunction.<sup>86</sup>

Adenosine receptors play important roles in life actions to keep the autonomic nervous system from operating abnormally. Through building an adenosine receptor knockout mouse model, the mechanism of acupuncture was revealed; namely, upregulation of adenosine effectively mediated the effects of acupuncture,<sup>128</sup> and this finding has been verified in human studies.<sup>129</sup> Acupuncture therapy for asthma has shown that the stimulation of GV14, BL13, and BL12 significantly inhibits adenosine cyclase to decrease cAMP/cGMP and relax airway smooth muscles<sup>86</sup> and inhibit histamine release from mast cells.<sup>130</sup> Stimulation of GV14, BL13, and BL12 also enhances the levels of SOD and GSH and lowers the level of MDA in the lung to relieve oxidative stress injury of the lung with asthma.<sup>45</sup> Another study has reported that acupuncture could also significantly reduce NO in the pulmonary tissue and bronchoalveolar lavage fluids.<sup>116</sup>

### Hormones

An HPA axis disorder is one of the vital factors in the pathogenesis of asthma and is also a factor that induces glucocorticoid resistance.<sup>131</sup> Epigenetic research on HPA has demonstrated that the lung overexposure to nicotine induces the reduction of  $\beta$ -endorphin and hypothalamic corticotropin-releasing hormone (CRH) of the offspring, while acupuncture for asthma significantly reverses the levels of CRH and  $\beta$ -endorphin.<sup>7</sup>

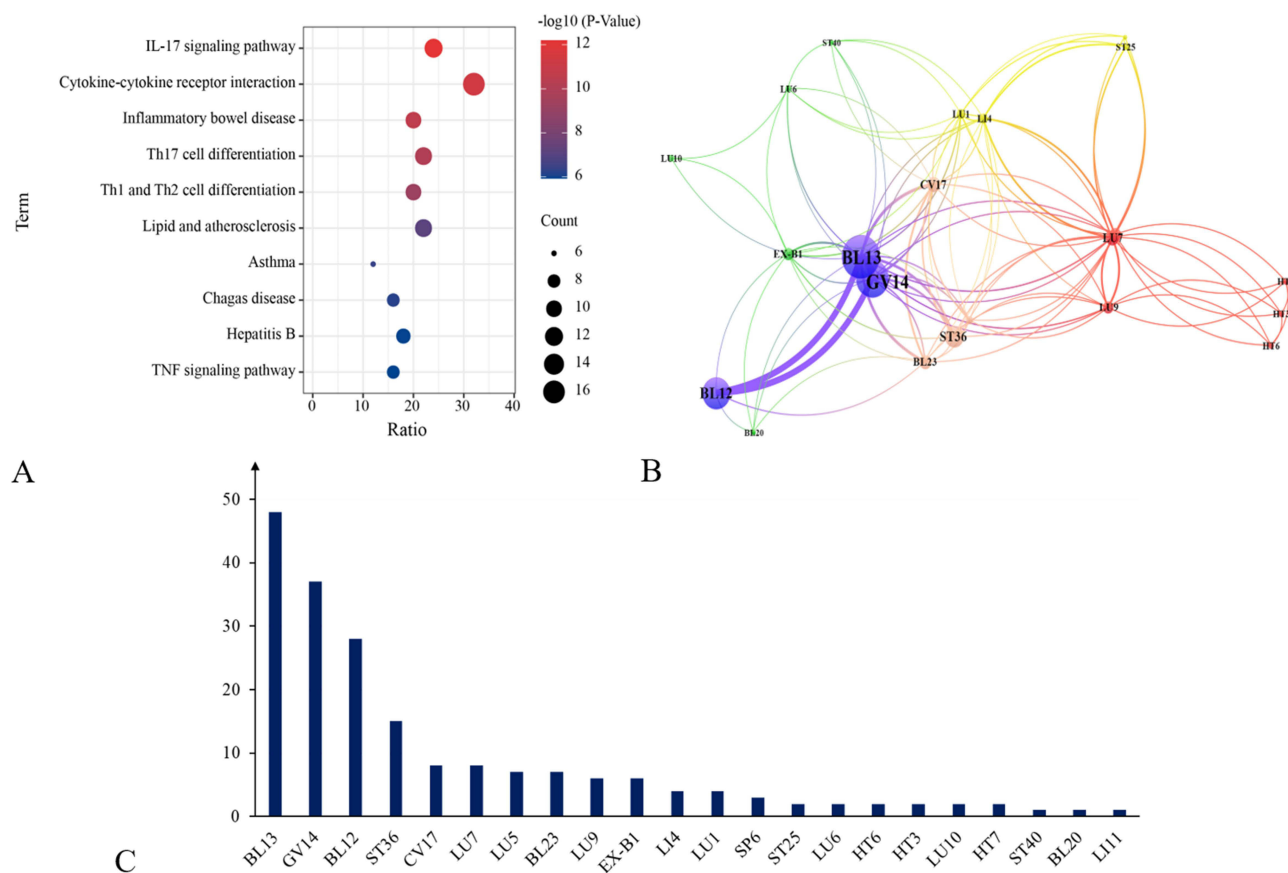
The level of CRH determines the secretion of adrenocorticotropic hormone (ACTH) and cortisol (CORT), which control inflammatory responses in asthma. Acupuncture at GV14, BL13, and BL12 can recover the levels of ACTH and CORT in serum based on the reduction of ACTH and CORT induced by asthma.<sup>97,98</sup>

## Analysis of the Retrieved Data

We subjected the retrieved data and associated proteins to bioinformatics analysis and standardized protein ID with UniProt (<https://www.uniprot.org/>), and we adopted enrichment analysis to obtain biological pathways in DAVID (<https://david.ncifcrf.gov/>). Then, association analysis was applied to determine the combination pattern of acupoints.

Analysis of biological pathways revealed that asthma was related to the IL-17 signaling pathway, cytokine–cytokine receptor interaction, Th17 cell differentiation, Th1 and Th2 cell differentiation, and TNF signaling pathway (Figure 6A). These pathways belong to the immune system, which shows that the pathogenesis of asthma is mainly attributed to dysfunctional immunity.

Analysis of acupoints formula revealed that 22 acupoints have been involved in asthma treatment, and BL13, GV14, BL12, and ST36 were widely applied in clinical practice (Figure 6C), especially ST36. Clinical practice and studies of acupuncture using infrared thermal imagers have revealed the biological mechanisms underlying clinical therapies for asthma based on the treatment of lung disease resulting from alterations in the composition of the gut microbiome,<sup>106</sup> providing evidence for the frequent selection of ST36 in the treatment of asthma.



**Figure 6** Data analysis of the collected data from literature.

The acupoint formula including BL13, BL12, and GV14 is a common formula in clinical practice, and the latest research has revealed that stimulation of these acupoints can enhance the FC between the right insula subregions and the brain regions related to default mode network in asthma patients, providing evidence for the effects of acupuncture therapy for asthma from the perspective of neuroscience.<sup>32</sup> ST36, BL23, CV17, and EX-B1 are essential auxiliary acupoints to enhance the acupoint formula efficacy. Besides the abovementioned formulas, another formula included LU7 and LU9 as primary acupoints and selected other auxiliary acupoints from the heart meridian, such as Shenmen (HT7), Shaochong (HT9), and HT6, as auxiliary acupoints to relieve asthma with yin deficiency syndrome (Figure 6B).

## Discussion

Complementary and alternative medicine (CAM), including acupuncture, is spreading in western countries. It has been reported that CAM can help children decrease the annual uptake of influenza vaccination.<sup>132,133</sup> Acupuncture therapy, one of the most commonly used alternative medicine tools, cannot form a standard guideline protocol due to the small sample size and significant bias of the randomized controlled trials of acupuncture for asthma, making it difficult to assess the quality of research on acupuncture.<sup>134</sup> Therefore, more high-quality studies are needed to clarify the duration of acupuncture, improvement of clinical symptoms, adverse effects, and even reactions related to immune mechanisms.<sup>23</sup> However, even with the above problems, a large clinical acupuncture trial has revealed that acupuncture therapy for allergic asthma improves health-related quality of life compared with no acupuncture therapy<sup>24</sup> and can even replace some placebos with side effects.<sup>135</sup> This indicates that acupuncture therapy as an effective measure of CAM can improve the clinical effects of anti-asthma drugs and relieve symptoms of asthma.<sup>136</sup>

Although the efficacy of acupuncture in relieving clinical asthma symptoms and in the treatment of asthma has been validated, clinical trials are currently limited to studying symptoms and do not focus on mechanisms. Clearly, this may be

a consequence of the difficulty in obtaining clinical samples, which has led to largely confining the study of mechanisms to animal models rather than humans. Second, due to the unitary means of modelling, most of them are OVA-induced animal models, which leads to unitary mechanism studies in animal experiments. The lack of diversity in animal models of asthma signifies that studies of acupuncture for asthma have focused mainly on GV14, BL12, and BL13, while research into other acupoints has stagnated. The diversity of genes determines that human pathogenesis cannot be a unitary mechanism, so the studies of asthma are facing a major problem, asthma subtype, which is another reason for the weakening or even disappearance of one of the reasons of the efficacy of inhaled corticosteroids.<sup>137–139</sup>

As a noninvasive test, fMRI is an effective solution for the dilemmas faced by both clinical and animal model studies. Current fMRI-based studies mainly focus on the analysis of functional connectivity (FC) in different brain regions and do not include the study of the material basis of acupuncture, resulting in neuromodulation not being able to be associated with the material basis, and this fragmented view is not conducive to the study of asthma and treating asthma with acupuncture. In the future, molecular mechanisms should be combined with neuromodulation studies, which could facilitate the studies of asthma subtype and the role of acupuncture in asthma treatment.

## Conclusion

Clinical and experimental studies have demonstrated the efficacy of acupuncture therapy, but have not yet elucidated the holistic nature of the neural response network, the correlations between nerves and their effector substances, and the changes in the substance base under the modulation of the neural network. Therefore, further research is needed to improve the use of acupuncture in clinical practice.

## Abbreviations

AHR, hyperresponsiveness; fMRI, functional magnetic resonance imaging; GR, glucocorticoid receptors; TCM, traditional Chinese medicine; WHO, World Health Organization; MRI, magnetic resonance imaging; PAG, periaqueductal gray; FC, functional connectivity; ILC2s, pulmonary group 2 innate lymphoid cells; ACC, anterior cingulate cortex; HPA, hypothalamus–pituitary–adrenal; dVMHC, dynamic voxel-voxel-mirror homomorphic connectivity; vAI, ventral anterior insula; dAI, dorsal anterior insula; PI, posterior insula; Ach, acetylcholine; SP, substance P; TSLP, thymic stromal lymphopoietin; ROS, reactive oxygen species; ASMCs, airway smooth muscle cells; BALF, bronchoalveolar lavage fluid; VCAM-1, vascular cell adhesion protein 1; ICAM-1, intercellular adhesion molecule 1; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow; ERS, Endoplasmic reticulum stress; PERK/eIF2, Proline-rich extensin-like receptor kinase/eukaryotic translation initiation factor 2A; IRE1 $\alpha$ /XBP1, endoplasmic reticulum-to-nucleus signaling 1/x-box-binding protein 1; ATF6 $\alpha$ /ERp57, activating transcription factor 6 alpha/endoplasmic reticulum resident protein 57; Grp78, 78-kDa glucose-regulated protein; VEGFA, vascular endothelial growth factor A; MUC5AC, mucin 5AC; PtdIns3K, phosphatidylinositol 3-kinase; NKA, neurokinin A; NKB, neurokinin B; CGRP, calcitonin-gene related peptide; VIP, vasoactive intestinal peptide; NGF, nerve growth factor; ASM, airway smooth muscle; OXs, Orexins; SOD, superoxide dismutase; GSH, glutathione; MDA, malonaldehyde; LTB4, leukotriene B4; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; NO, nitric oxide; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; CORT, cortisol; CAM, Complementary and alternative medicine.

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## Disclosure

The authors report no conflicts of interest in this work.

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