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Review article

An underlying mechanism behind interventional pulmonology techniques for refractory asthma treatment: Neuro-immunity crosstalk

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ABSTRACT

Asthma is a common disease that seriously threatens public health. With significant developments in bronchoscopy, different interventional pulmonology techniques for refractory asthma treatment have been developed. These technologies achieve therapeutic purposes by targeting diverse aspects of asthma pathophysiology. However, even though these newer techniques have shown appreciable clinical effects, their differences in mechanisms and mutual commonalities still deserve to be carefully explored. Therefore, in this review, we summarized the potential mechanisms of bronchial thermoplasty, targeted lung denervation, and cryoablation, and analyzed the relationship between these different methods. Based on available evidence, we speculated that the main pathway of chronic airway inflammation and other pathophysiologic processes in

Abbreviations: GINA, Global Initiative for Asthma; M receptor, muscarinic receptor; CNS, central nervous system; LAMA, long-acting anticholinergic drug; ICs, inhaled glucocorticoids; LABA, long-acting β2 receptor agonists; IP, interventional pulmonology; AHR, airway hyperreactivity; FDA, Food and Drug Administration; BALF, bronchoalveolar lavage fluid; HSP60, heat shock protein 60; PRMT1, protein arginine methyltransferase-1; ASM, airway smooth muscle; OXPHOS, oxidative phosphorylation; RANTES, regulated upon activation, normal T-cell expressed and secreted; TRAIL, tumor-necrosis factor-related apoptosis-inducing ligand; TGF-β1, transforming growth factor-β1; TLD, targeted lung denervation; COPD, chronic obstructive pulmonary disease; HBR, Hering-Breuer reflex; ChAT, choline acetyltransferase; M3R, M3 receptor; BCD, bronchial cryodenervation; ACh, acetylcholine; N receptors, nicotinic receptors; MHC-II, major histocompatibility complex II; Th2, type 2 helper T cell; IL, interleukin; DC, dendritic cell; TSLP, thymic stromal lymphopoietin; ILC2, type-2 innate lymphoid cell; RAR, rapidly adapting mechanoreceptor; SAR, slowly adapting mechanoreceptor; H_2S, hydrogen sulfide; NSAID, nonsteroidal anti-inflammatory drug; PGE2, prostaglandin E2; TRP, transient receptor potential; TRPA1, transient receptor ankyrin 1; NG, nodose; DRG, dorsal root ganglion; TG, trigeminal ganglion; CRISPR, clustered regularly interspaced short palindromic repeats; OVA, ovalbumin-induced asthma; VIP, vasoactive intestinal peptide; SP, substance P; CGRP, calcitonin gene-related peptide; VIPR2 or VPAC2, VIP receptor type 2; HDM, house dust mite; NPY, neuropeptide Y; CRH, corticotropin-releasing hormone; α7AChR, α7 nicotinic acetylcholine receptor.

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asthma is sensory nerve-related neurotransmitter release that forms a "neuro-immunity crosstalk" and amplifies airway neurogenic inflammation. The mechanism of completely blocking neuro-immunity crosstalk through dual-ablation of both efferent and afferent fibers may have a leading role in the clinical efficacy of interventional pulmonology in the treatment of asthma and deserves further investigation.

1. Introduction

Asthma, a common disease that seriously threatens health at all ages, is clinically characterized by recurrent wheezing, chest tightness, and dyspnea accompanied by widely variable reversible airflow limitation, which may resolve spontaneously or in response to medication in most patients. Currently, asthma affects 1–18 % of the population in different countries, as described in the Global Initiative for Asthma (GINA) 2022. According to data from the Global Burden of Disease Study 2017 published in the Lancet [1] in 2017, nearly 550 million people had a chronic respiratory disease, and asthma was the second leading cause worldwide.

Regularly inhaled glucocorticoids and bronchodilators are recommended as treatment options, in addition to macrolide antibiotics and biologically targeted agents such as anti-IgE monoclonal antibodies. With the improvement of the living environment and the increased awareness of personal health, most patients can receive standardized drug therapy and management, and obtain appreciable symptom control. However, there still exists a considerable proportion of patients whose symptoms remain ineffectively controlled after receiving the standard inhaled therapy (GINA steps 4–5), which is referred to as refractory asthma. Some studies [2,3] pointed out that the prevalence of current asthma over age 20 years is 4.2 %, whereas refractory asthma forms account for 15.5 % of the asthma population, manifesting as reduced quality of life and requiring high-dose medication maintenance with a high burden of disease. Faced with this reality, there has been a continuous effort to develop and create new drugs or new approaches to asthma treatment intending to reverse the quandary faced by asthma management.

In this review, we will summarize the potential mechanism of interventional pulmonology techniques in refractory asthma treatment. We will also deduce the relationship between these different methods, therefore better understanding the secret of the underlying mechanism behind the interventional pulmonology techniques for refractory asthma treatment.

2. What is the Current Management Deficit in Refractory Asthma?

2.1. Asthma pharmacotherapy implications

As early as the 1980s, drugs against cholinergic nerves were applied clinically. Although some efficacy was obtained in some patients, their use in the clinic was limited due to the nonselective effects of atropine on muscarinic receptors (M receptors) used early on, including its propensity to cause many adverse effects, such as dry mouth, sticky sputum, and central nervous system (CNS) excitation. The subsequently used ipratropium bromide was also gradually replaced by the long-acting anticholinergic drug (LAMA) tiotropium, which is highly selective for M1 and M3 receptors and has a long duration of action suitable for once daily administration. In the 2022 edition of the GINA guidelines for asthma control, inhaled glucocorticoids (ICs) with long-acting β2 receptor agonists (LABA) and LAMA combination therapy (as triple therapy) is recommended for refractory asthma. This triple therapy was demonstrated to effectively improve patients' pulmonary function and reduce the occurrence of acute exacerbations [4].

Nevertheless, there remains the dilemma that a significant proportion of patients with refractory asthma still do not achieve effective control of their symptoms, even after medical therapeutic intervention with triple therapy. This suggests that blocking acetylcholine released by vagal efferent fibers from binding to M receptors on effector cells has an unsatisfactory efficacy despite providing some therapeutic benefit, and it is highly likely that other pathways of vagal action exist.

2.2. Asthma nonpharmacologic therapy development

Nonpharmacologic means of intervention have also been used during the journey to intervention of vagal tone for the treatment of refractory asthma. In 1930, Professor Rienhhoff's group [5] was the first to surgically ablate the vagus nerves to interrupt the effects of increased vagus nerve excitability in patients with asthma. A total of 21 patients with refractory asthma were included, and their vagal trunks innervating the bronchus and lung were blocked at the right and left hilum. The results showed that multiple refractory asthmatics had different degrees of improvement in their asthma exacerbation frequency and quality of life after treatment. In 1957, Balogh's team [6] treated 19 patients with refractory asthma using pulmonary vagotomy, and the postoperative pulmonary function and sputum hypersecretion were effectively improved in patients. In 1963, Professor Colebatch's team at the University of Sydney [7] further implemented bilateral vagal blockade in sheep, and the results confirmed that disrupting the vagus nerve was effective in reducing airway resistance under physiological conditions. Multiple animal studies have since demonstrated that vagal denervation effectively alleviated the pathophysiological phenomena of pulmonary mucus hypersecretion and increased airway resistance in asthmatic states. However, such procedures were accompanied by significant surgical trauma and technical complexity combined with relatively high complication rates and lethality in the perioperative period, and failed to be clinically acknowledged.

After entering the 21st century, with the rise of interventional pulmonology (IP), a variety of novel, bronchoscopy-guided, minimally invasive interventional treatment techniques for refractory asthma emerged, including bronchial thermoplasty, targeted

lung denervation, and cryoablation. These technologies achieve their therapeutic effects by targeting important aspects of asthma pathophysiology, such as airway smooth muscle, epithelium, and nerves. Although these therapies have already demonstrated appreciable clinical effects, their different mechanisms and mutual commonalities still deserve to be carefully examined.

3. What lies behind current interventional pulmonology for asthma?

3.1. Potential mechanisms of bronchial thermoplasty

As original designed, bronchial thermoplasty focuses on destroying airway smooth muscle (ASM) to help decrease airway narrowing and bronchospasm, leading to the control of asthma and improved respiratory function [8]. Its ability to cause ASM destruction has been demonstrated in dogs [9], cows [10], and humans [11]. Since 2006, a tremendous amount of research data [12–17], from trials to actual clinical applications, demonstrated the of bronchial thermoplasty, including a reduction in airway hyperreactivity (AHR), improved lung function, relief of asthma symptoms, and fewer acute exacerbations. These data confirmed the safety and effectiveness of bronchial thermoplasty in clinical situations and was approved by the Food and Drug Administration (FDA) in 2010, and the long-term followup ($BT10^{+}$ study) [18] further support it popular acceptance. Bronchial thermoplasty is a highly suitable option for patients with airflow obstruction caused by ASM hypertrophy. It offers the advantage of rapidly and durably opening up narrowed airways, resulting in improved airflow dynamics and gas exchange.

However, from a review of published literature, the underlying mechanism of bronchial thermoplasty may not only rely on reducing ASM. As Langton's team demonstrated through body plethysmography, after procedure, the residual volume was reduced, followed by a reduction of gas trapping [19]. They further found that this change in residual volume was also related to a reduction in airway resistance and patient symptoms, but these effects as investigated in their study were considered to result from the reopening of small airways [20]. Interestingly, Bronchial thermoplasty is only applied at the proximal level in the main bronchi and cannot reach the small peripheral airways, which is a significant aspect of the pathogenesis of asthma, and thus causes scholars to speculate whether there are other mechanisms in this process, thus raising our interest in discussing this further.

In fact, the incidental findings in the tissue not directly treated by bronchial thermoplasty, i.e., tissue other than the airway smooth muscle, previously caught the attention of physicians. According to the comments by Bonta et al. [21] in 2015, bronchial thermoplasty may hide some mechanisms beyond the traditionally recognized ones. An early observational study [22] found that not only was there a reduction in ASM in biopsies of treated airways, but also, and strangely, there was a decrease in the non-treated middle lobe. Bonta and colleague proposed that the radio-frequency energy emitted by bronchial thermoplasty spreads its heat shock effect beyond the directly treated airway through incomplete fissures. They also thought that the transient radiology abnormalities around the non-treated middle lobe supported this hypothesis, but did not provide a definite conclusion at that time. The same radiological abnormalities following bronchial thermoplasty were also found by Debray et al. [23] and d'Hooghe et al. [24].

The cause of untreated lobe radiological abnormalities are divided into three main explanations [25]: 1) diffusion of heat shock along the bronchial tree, which might be related to the earlier reported decrease in the ASM area in the non-bronchial thermoplasty-treated middle lobe [22]; 2) extension of heat shock through (incomplete) fissures to an adjacent lobe [23]; or 3) blood, secretions, and mucus flowing from the bronchial thermoplasty-treated upper lobes down to the dependent lower lobes, causing ground glass opacities to be observed in distal areas [25]. However, there is no final conclusion at present, but the majority of researcher prefer the heat shock "aftermath" theory and assume that the untreated tissue is affected in this manner.

In 2019, Sun et al. [26] first demonstrated the possible bronchial thermoplasty heat shock-regulated signaling pathway. They collected bronchoalveolar lavage fluid (BALF), primary bronchial epithelial cells, and fibroblasts from patients before and after bronchial thermoplasty, and then conducted proteome and transcriptome analyses with other analyses. Their research found that epithelial cell-derived heat shock protein-60 (HSP60) was the main mediator and regulated protein arginine methyltransferase-1 (PRMT1) expression. The bronchial thermoplasty procedure modified the epithelial cells, reducing HSP60 secretion and subsequent PRMT1 expression, and thereby suppressed airway fibroblast remodeling. In 2021, the team published another related work [27], demonstrating that bronchial thermoplasty also increased the expression of HSP70 and HSP90 in epithelial cells. The expression of the glucocorticoid receptor also increased after bronchial thermoplasty, and by binding with HSP70 and HSP90 as a complex, the receptor was able to achieve a high affinity for steroid binding, possibly further improving the therapeutic effect of glucocorticoid inhalation therapy postoperatively.

These two studies also pointed out one thought-provoking idea: although bronchial thermoplasty prevents airway contracture caused by ASM, it is only one element of the entire therapeutic mechanism, and another candidate is bronchial epithelial cells. The bronchial epithelium is the most superficial airway wall layer exposed to the radio-frequency heating energy of bronchial thermoplasty, which has been shown to result in epithelial sloughing as detected by optical coherence tomography directly after bronchial thermoplasty [28,29].

Abilash's research [30] supported that, compared with a healthy control group and mild asthma group, the bronchial epithelial cells of severe asthma patients had a significant reduction of the oxidative phosphorylation (OXPHOS) gene and upregulation of fatty acid metabolism-related genes. However, after the bronchial thermoplasty procedure, this situation was reversed, which suggests that bronchial thermoplasty partially normalized the metabolic difference, thus resetting the bronchial epithelial cells. This finding to some extent reveals the epithelial-related immune mechanism of asthma treated by bronchial thermoplasty, which may relate to previous studies [31–33].

This immune mechanism of various chronic diseases and its character in bronchial thermoplasty treatment has long been a focus. There is no doubt that ASM is one source of chemokines and pro-inflammatory factors, and therefore it is rational to identify the

changes in the levels of these mediators. As first demonstrated by Denner et al., in 2015 [34], the BALF before and after bronchial thermoplasty showed different trends. Transforming growth factor-β1 (TGF-β1) and regulated upon activation, normal T-cell expressed and secreted (RANTES)/CCL5 were decreased, while cytokine tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL) substantially increased. In 2017, Malovrh et al. [35]. published a research letter about the first exploration of bronchial thermoplasty-treated patient pulmonary T lymphocyte changes. A two-fold increase in the proportion of $CD4^+$ $CD25^+$ Treg cells in the BALF was found, while they also noticed that the proportion of cytotoxic $CD3^+CD8^+$ cells decreased. What they found shed light on the fact that bronchial thermoplasty not only caused changes in ASM itself, but also partly suppressed the asthma inflammatory response (such as Treg cell depletion), further benefiting patients.

Since ASM and airway epithelium both undergo changes following bronchial thermoplasty, the peripheral cholinergic nerves and other structures which are distributed in the bronchi may also potentially have a functional role in the underlying bronchial thermoplasty mechanism. An extremely important study connected nerves and immunity in this process. Pretolani et al. [36] first explored the link between the structural changes induced by bronchial thermoplasty and improvement of severe asthma control. They studied 15 patients with severe uncontrolled asthma who underwent bronchial thermoplasty, and found that the following decreased: the ASM area, subepithelial basement membrane thickening, number of submucosal and ASM-associated nerve fibers, and number of epithelial neuroendocrine cells from baseline, and that these structures were highly correlated with clinical efficacy. More interestingly, the same effects were observed in the untreated middle lobe. Furthermore, in their research, neither the bronchial epithelium, blood and lymphatic vessels, subepithelial mucous glands, eosinophils, neutrophils, goblet cell hypertrophy, or hyperplasia were significantly modified by bronchial thermoplasty. Other than traditional changes in the ASM, these findings indicated that bronchial thermoplasty may regulate airway status (excitability and immune response) by affecting the airway autonomic nerves or impacting neuroendocrine secretions. By obtaining biopsies on the segmental and subsegmental bronchial carina at the end of each procedure and 12 months after the procedure, Facciolongo et al. [37] supported that the bronchial thermoplasty ablation effect on the reduction of total nerve fiber scores was founded in the submucosa and ASM. They also detected the inflammatory cell level during the 1-year follow-up, which showed that macrophages ($CD68^+$ cells) were the only inflammatory cells that remained higher after treatment. Facciolongo suggested that bronchial thermoplasty may interrupt C fiber nerve endings, blocking the centrally-mediated reflex-caused asthma symptoms. (A detailed mechanism of bronchial thermoplasty can be seen in Fig. 1).

In short, bronchial thermoplasty continuously releases heat energy, mainly targeted on ASM, that may also potentially alter other airway structural components other than ASM, assisting the clinical efficacy. The hidden mechanism is still waiting to be explored. Whether neuro-immunity influenced by bronchial thermoplasty contributes to the observed clinical efficacy is still poorly understood.

3.2. *Potential mechanisms of targeted lung denervation*

Targeted lung denervation (TLD) is another interventional pulmonology technology that focuses on chronic obstructive pulmonary disease (COPD), but also has certain referential significance in asthma. It is based on the hypothesis that cholinergic tone is abnormally increased in COPD patients [38], and the secreted acetylcholine induces airway and bronchial constriction and mucous hypersecretion by binding with M3 receptors [39,40]. TLD treatment, using a bronchoscopy-guided radio-frequency catheter, ablates the airway

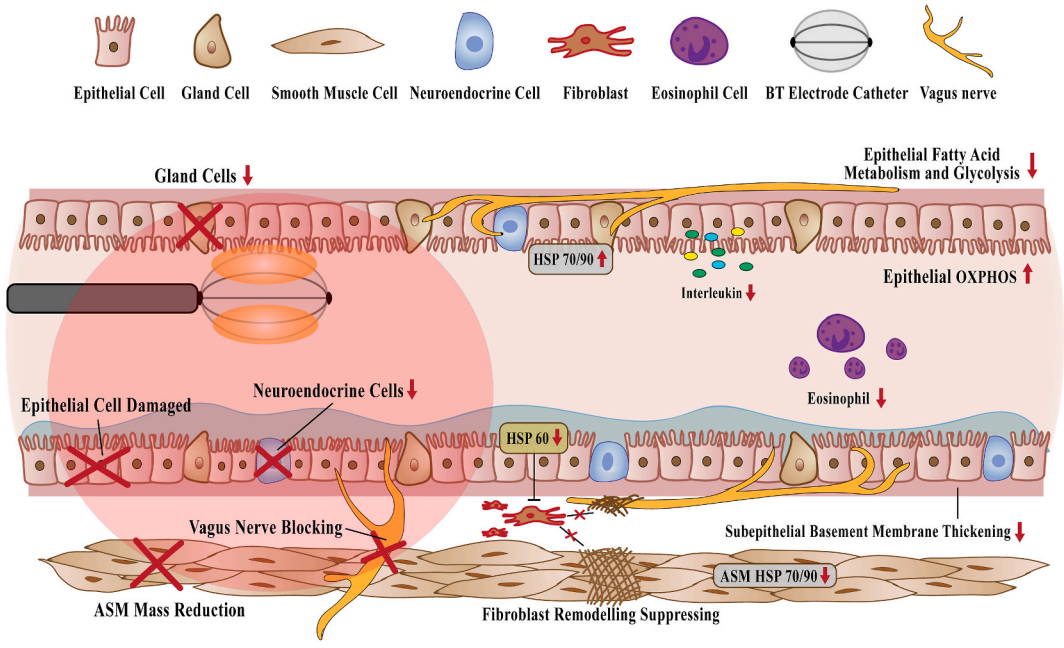

Fig. 1. Schematic diagram of the mechanism of bronchial thermoplasty.

nerves that travel parallel to and outside of the main bronchi and into the lungs. After preclinical studies on sheep [41] demonstrated its effectiveness in the destruction of cholinergic airway nerves without affecting epithelial integrity or the esophagus, the team soon started a pilot study [42] and subsequently AIRFLOW [43,44] and AIRFLOW2 [45,46] trials further demonstrated that TLD improves lung function and quality of life in patients with sustained effects. TLD is appropriate for patients without organic pathological obstruction but with bronchoconstriction resulting from abnormal excitation of the vagus nerve. Another advantage of TLD is its capacity to effectively decrease mucous secretion, thereby mitigating small airway blockage.

Some questions had been raised due to a previous animal study of COPD that found that acetylcholine also plays a role in airway inflammation and remodeling [39]. Kistemaker et al. [47] wondered, by applying TLD, whether the pro-inflammation effects of acetylcholine and the vagus nerves could be blocked. Seven moderate-to-severe COPD patients were recruited, and their BALF was tested before and after (30 days) denervation. Results from this study showed that TLD decreased the levels of neutrophils and cytokines such as IL-8 and CCL4 (MIP-1β) in the patient's BALF, while the gene expression of IL-8, IL-6, TGF-β, and MUC5AC also decreased. Meanwhile, Srikanthan's team [48] conducted whole-transcriptome sequencing of mucosal brush samples, revealing a notable decrease in the expression of acetylcholine-related genes on the mucosal epithelium following TLD. There were also observed trends in the downregulation of genes associated with immunity and inflammation, particularly those involved in the ubiquitin-proteasome system. This suggest a potential link between TLD-induced nerve denervation and the observed changes in airway inflammation and oxidative stress, which could contribute to the reduction of exacerbations in COPD. However, these exploratory studies has their own limitations. Denervation caused by radiofrequency not only targets the cholinergic nerve but also influences sensory nerves. Whether other neurotransmitters in addition to acetylcholine were changed, further leading to airway neurogenic inflammation suppression, is still a worthy direction to investigate.

In 2018, Hummel and colleagues again assessed the histologic effects of TLD on eleven sheep and two dogs [41,49]. The TLD gross effects on bronchial and peribronchial structures were similar to their team's previous results in 2014 [41] but included more details. A nearly 30 % decrease in pulmonary resistance and a blocked Hering-Breuer Reflex (HBR) were found, while the tissue 1 cm around the ablation area was not apparently damaged. Immunohistochemical analysis after therapy showed that the expression of neurofilaments of motor and sensory axons on bronchial peripheral nerves was lost, and was accompanied by fibrosis of vagus nerve branches located on adventitial layers of the bronchi. Sensory fibers innervated nearly the entire bronchi, while the sensory receptors and bipolar vagal sensory neurons responded to stimuli and regulated breathing and bronchoconstriction/dilatation [50–52]. The loss and restoration of the HBR may be related to the sensory axons that regenerated faster compared with motor axons [53]. Therefore, it can be reasonably assumed that vagus sensory nerves were also ablated during the targeted lung de-"vagus"-nervation. Whether the anti-inflammatory effects of TLD were induced by sensory nerve-derived neuropeptides are debatable.

Two years later, the same team published a long-term (640 days) study on the TLD effects on the sheep vagus nerve [54]. In addition to some fibrosis that was consistently observed through the outer layers, other damaged tissue (bronchial epithelium, wall, cartilage, and alveolar parenchyma) nearly recovered compared to before the procedure. Efferent and sensory axons quantified by a pan-neuronal marker of neurofilaments showed that the TLD treatment site and distal nerves were restored to the proximal level at the 365-day follow-up, while the main trunks of the vagus nerve were unaffected. The team further evaluated the treatment site, including

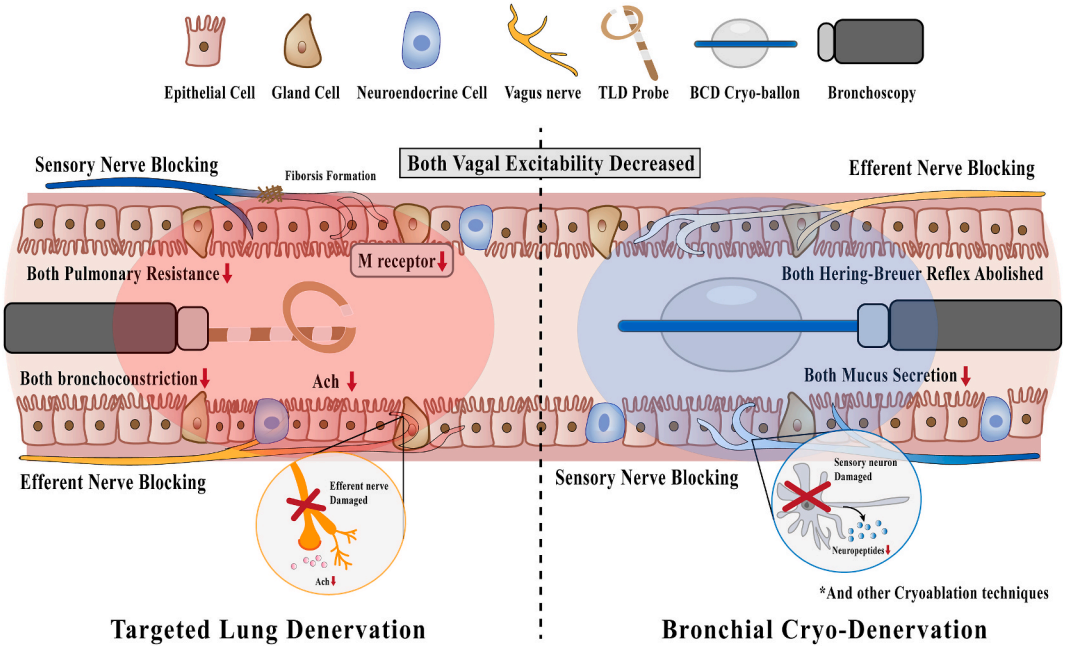

Fig. 2. Schematic diagram of the mechanism of targeted lung denervation and bronchial cryo-ablation.

efferent axon disruption and regeneration with choline acetyltransferase (ChAT) and used an untreated airway as a control. ChAT expression was markedly reduced at 365 days and this reduction was sustained for 640 days, demonstrating a long-term absence of regeneration after TLD. Fibrosis and scar formation after radiofrequency may account for the impeded nerve regeneration, including both afferent and efferent fibers. Interestingly, this study counted total nerves using a pan-neurofilament marker of a cytoskeletal protein that represents structure for both afferent and efferent axons, and then assessed efferent nerves alone by ChAT, a protein that exclusively concentrates in acetylcholine-producing cells and efferent neurons. By calculating the difference through this method, the research team speculated that although sensory axons were blocked after TLD, they regenerated at a faster rate. Unfortunately, whether the sensory neuron and its function changed during the TLD still lacks a specific analysis and conclusion. While the effects of epidermal growth factor receptor [55,56] and nerve growth factor [57,58] on sensory nerve regeneration and neuropeptide after ablation also deserve exploration. (The detail mechanism of TLD and BCD can be seen in Fig. 2).

In summary, targeted lung denervation also continuously releases heat energy, but mainly targeted on bronchial vagal nerve fibers, mimicking long-acting pharmacologic blockade effects, and has already produced a positive clinical impact [59]. There has been a recent gradual transition in its application from COPD to asthma [60] and chronic bronchitis [61]. However, the potential afferent nerve mechanisms require further elucidation. Significantly, neuro-immunity and related airway neurogenic inflammation influenced by this interventional pulmonology technology is probably a point that has been largely ignored.

3.3. Potential mechanisms of cryoablation

Cryotherapy is a widely used interventional pulmonology technique that includes the process of cooling, freezing, and thawing, thereby resulting in irreversible damage to the target structure from significantly low temperatures. Traditional applications of cryo-energy mainly focused on biopsy, foreign body extraction, and airway occlusion treatment, and was recently extended to ablation areas. Compared with thermal radio-frequency ablation, cryoablation causes less of a local inflammatory reaction and fibrosis in the airway, leading to minimal side effects on adjacent normal mucosa and cartilage, while also inhibiting the growth of granulation tissue [62,63]. The attributes of cryoablation render it well-suited for patients who are susceptible to granulation tissue proliferation and scar formation, which can subsequently lead to airflow limitation.

Li et al. [64] tested the cryoablation technique for blocking airway remodeling and compared its effectiveness to bronchial thermoplasty. They chose the beagle dog as the model and found that the bronchial thermoplasty group and cryoablation group showed the same trends of a decreased ASM thickness and decreased average optical density of the M3 receptor (M3R) compared to the control group, while no significant difference was found between the bronchial thermoplasty group and cryoablation group, demonstrating the value of cryo-energy in ASM ablation. Although this study did not include any molecular mediator or immunological analyses, we can still speculate that the cryoablation may similarly delay airway remodeling not only by shaving ASM [65], but also by regulating the expression of the smooth muscle muscarinic receptor M3R as a neural mechanism, and thus attenuating contraction of the ASM, decreasing sputum secretion, and reversing airway remodeling.

Cryoablation was also shown to be effective in treating refractory hypertension [66] and paroxysmal atrial fibrillation [67] by destroying the sympathetic nerve or vagus nerve of the renal artery or heart, respectively, while our team's previous work broadens its application sphere to lung vagus nerves. We proposed a cryo-balloon-targeted lung denervation system and a procedure called "bronchial cryo-denervation" (BCD) [68]. We first confirmed its feasibility and safety in the preclinical stage as a substitute for anticholinergic inhaler therapy. By performing the procedure on twelve sheep, airway resistance alterations, the HBR, and histological and immunohistochemical parameters were evaluated. A large number of axons showed vacuolization, while some showed necrosis, indicating axon disruption. Physiological assessment of denervation by comparing airway resistance and HBR also supported the success of vagus nerve blocking. Furthermore, this bronchoscopy-guided interventional pulmonology technique required a shorter operation time and caused less denervation-induced damage to adjacent tissues, and therefore is particularly suitable for asthma patients for whom airway hyperresponsiveness is caused by intervention. Further exploration is continuing in a clinical trial for asthmatic patients and is showing good initial clinical efficacy. However, we recognize that the exact mechanism of our BCD, a new technology for refractory asthma, is still not very clear (Fig. 2).

Summarizing, more in-depth elucidation of the relationship of IP with neuro-immunity in bronchial thermoplasty, TLD, and cryoablation is therefore highly warranted to lay a solid theoretical foundation for further clinical extension of this new technology in interventional pulmonology.

4. What mechanisms underlie asthma that deserve renewed attention?

4.1. Rethinking the role of the vagus nerve in asthma

The respiratory system is innervated by autonomic nerves, which include sympathetic and parasympathetic nerves. The sympathetic (adrenergic) nerves arise from the thoracic segments 2–4 of the spinal cord, from which preganglionic fibers emanate, and exchange neurons in the cervical ganglia of the sympathetic trunk. Postganglionic fibers are mixed at the hilum with cholinergic nerves and distributed to the trachea, bronchi, and the lungs. The parasympathetic (cholinergic) nerves originate from the dorsal nucleus of the vagus and exchange neurons near the innervating organs via the vagus nerve to reach the trachea, bronchi, and lungs. Lung and bronchial, therefore are dually innervated by sympathetic and parasympathetic fibers. Parasympathetic excitation acts on cholinergic receptors on effector cells, namely muscarinic receptors (M receptors) and nicotinic receptors (N receptors), by releasing acetylcholine (ACh). ACh acts on M1 and M3 receptors mainly distributed on airway smooth muscle cells and submucosal glandular cells, leading to

contraction of smooth muscle cells and mucus secretion from the glands [39,69–71].

Cholinergic parasympathetic nerves have long been recognized to play a significant role in asthma [71,72], but the traditional view only focused on their function of smooth muscle spasm, mucous plug formation, and other typical asthma-like symptoms [69,73]. Subsequently, some scholars found that M receptors were also present on inflammatory cells such as macrophages, eosinophils, neutrophils, and lymphocytes. When M3 receptors are activated by ACh, this can induce inflammatory cells to produce a variety of inflammatory factors and chemokines, which exacerbates the inflammation of asthmatic airways.

At the same time, studies have found that M3 receptors were also expressed on airway epithelium and fibroblasts. Neurogenic ACh as a neurotransmitter not only triggers airway smooth muscle contractions but is also closely associated with increased smooth muscle cell mass and excessive deposition of extracellular matrix, resulting in airway structural remodeling [73]. Drake et al. [74] found that both the length of ganglia and the number of branches of the vagus nerve in the lungs were significantly increased in patients with asthma compared with healthy controls, effectively demonstrating at a structural level that heightened excitability of the vagus nerve is present in asthmatic patients. However, a more interesting finding in this study that should be noted is the change in a different neurotransmitter: the amount of neuropeptide substance P (SP).

Some studies also supported that the parasympathetic nerves showed pro- or anti-inflammatory effects in the airway by releasing neurotransmitters from the peripheral endings of conducting primary sensory neurons [75]. Combining this finding with the above mentioned discoveries in bronchial thermoplasty, TLD, cryoablation, and other IP means, the change of the status of the parasympathetic nerve and neuroendocrine cells in asthma may be closely related to the therapeutic effect. Thus, maybe it is time to rethink of the role of the vagus nerve in asthma, especially its function on neuro-immunity mechanisms caused by vagal-released neurotransmitter.

4.2. Airway neurogenic inflammation in asthma

Inflammation is a protective response to different stimuli, both endogenous and exogenous. The concept of neurogenic inflammation was first discovered in the late 19th century by Bayliss [76], who found that electrical stimulation of dorsal roots induced cutaneous vasodilation. Early studies of neurogenic inflammation mostly centered on the skin, according to the observation that mammals produced neurogenic vasodilation in response to noxious stimuli [77,78]. Subsequent research demonstrated that this process provided more complex biological regulation of the somatosensory, immune, autonomic, and vascular systems, and caused plasma protein extravasation, immune cell infiltration, and other effects. On the basis of these mechanisms, researchers realized that neurogenic inflammation was not restricted to the skin [79] but also contributed to disease in other organ, such as migraine [80], arthritis [81], endometriosis [82], and asthma [83].

According to the traditionally accepted concept, after entering the airway, allergens are first intercepted by the airway epithelium (one target that can be influenced by bronchial thermoplasty), and form a complex by binding to the major histocompatibility complex II (MHC-II) on antigen-presenting cells (dendritic cells (DCs) and macrophages). Then, the complex is transported to the local lymph nodes where it binds to T cell surface receptors, guiding the naive T cells to polarize towards type 2 helper T cells (Th2), and activating the later Th2 cells to secrete interleukins (IL-3, IL-4, IL-5, and IL-13) and other cytokines, which in turn cause the characteristic asthma airway inflammation [84].

Recent studies have found that allergens also directly act on airway epithelial and DCs, activating the release of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), and induce type-2 innate lymphoid cell (ILC2) proliferation and activation. Activated ILC2s produce IL-5, IL-9, and IL-13, which mediate Th2 immune-inflammatory responses [85], and also act on nociceptors on vagal afferent fibers (which can be influenced by both bronchial thermoplasty and TLD). After sensory neuron stimulation, the signal transmits back to the periphery via circuitry that involves a relay neuron in the spinal dorsal horn, the so called “dorsal root reflex” [86]. With both the axons and the dorsal root reflex, the back propagating action potentials reaching the peripheral terminals of nociceptive nerve fibers produce a release of neurotransmitter such as acetylcholine, cytokine, and neuropeptide, in which the latter further stimulates $CD4^+$ T cells and ILC2 to form an inflammatory signaling circuit. This amplifies the effect of the Th2 cell secretions, and recruits a large number of eosinophils and other inflammatory effector cells, eventually resulting in the airway neurogenic inflammation of asthma [87,88].

Thus, in order to better understand and intervene in the airway neurogenic inflammation process in asthma, it is necessary to clarify the initiation phase and intermediate phase of this pathway.

4.3. Neurogenic Inflammation Induced by Sensory Neurons on Afferent Nerves

Innervation of sensory nerves is largely derived from parasympathetic (vagal) afferent nerves, with endings located near the lung parenchyma and airways [89], where noxious stimuli such as allergens, irritants, and pathogens are quickly detected [90,91]. Sensory nerves can be further divided into rapidly adapting mechanoreceptors (RARs), slowly adapting mechanoreceptors (SARs), and C fiber afferents [92,93]. Small-diameter unmyelinated C fibers serve as the main afferent nerves in the lung and airways, which present a variety of receptors and channels in their termini that are responsible for chronic or slow pain and other types of stimuli [94,95]. Sensory neurons on the C fiber influence the respiration rate, regulate airway tone, and induce airway neurogenic inflammation [83]. The signals perceived by the sensory neurons are various, including exogenous acetaldehyde, hydrogen sulfide (H2S), nonsteroidal anti-inflammatory drugs (NSAIDs), naringin, and some anesthetics. C fibers can also be the target of endogenous factors, such as cytokines, interleukins, fatty acids, and peptides, and inflammatory mediators, such as bradykinin and prostaglandin E2 (PGE2) [96–100].

After sensory neurons of an afferent nerve are stimulated, the activation and signal transmission acts through specific receptors

embedded in the fiber membrane of the sensory neurons. When the receptor binds to the above-mentioned activating factors, the structure of the protein will change, the ion channel transforms into an activated status, and extracellular cations (mainly Ca^{2+}) will enter the cell to create a Ca^{2+} influx. Various neuropeptides are subsequently released, inducing airway neurogenic inflammatory phenomena such as vasodilation, inflammatory cell exudation, mucosal congestion and edema, and bronchoconstriction [87](Fig. 3). Recent research demonstrated that this process is closely related to the small diameter sensory neurons (or C nociceptors) expressing members of the transient receptor potential (TRP) family [97], especially TRPA1 [101].

4.4. The initiation role of TRPA1 in asthma

Among the membrane receptors contributing to the transduction of noxious signals on afferent nerve endings, the transient receptor potential (TRP) family of ion channels is the largest one that can be found in diverse species. Based on the amino acid sequence homology, TRP channels can be divided into seven types, including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPN (Drosophila NOMP-C), and TRPA (ankyrin). They all contain six transmembrane domains, and are non-selective for cations [102,103].

Recent research focus of the TRP family is the transient receptor ankyrin 1 (TRPA1), a channel composed of a 33-amino-acid motif in the N-terminal domain [104]. TRPA1 is the sole member of the TRPA subgroup in mammals, which was first isolated from human fibroblasts in 1999 (formerly named ANKTM1) [105]. Later research found that it was expressed in a subset of TRPV1-expressing small-diameter nociceptive neurons and originated from the nodose, dorsal root, and trigeminal ganglia (NG, DRG, and TG, respectively) [106–108].

Asthmatic airway inflammation and its pathophysiology is initiated by TRPA1-expressing lung primary afferent fibers from the vagal nerve, TG and DRG [101]. Numerous exogenous, sometimes airborne irritants and endogenous irritants can activate TRPA1, which is known to aggravate asthma symptoms. Upon activation, TRPA1 induces neurotransmitter secretion from peripheral nerve terminals, which serve as the key initiators between the immune and nervous system crosstalk.

Targeted regulation of TRPA1 has been carried out in many studies. Pharmacological channel inhibition or genetic ablation of TRPA1 blocked allergen-induced leukocyte infiltration in the airways, reduced cytokine and mucus production, and decreased airway hyperreactivity [109]. However, blocking TRPV1 was less effective [109,110]. Rebecca et al. [111] adopt clustered regularly interspaced short palindromic repeats (CRISPR) technology to generate a *Trpa1* KO rat model. Results of this study showed that *Trpa1*--lacking rats in an ovalbumin-induced asthma (OVA) model had a weak inflammatory response and recruited fewer immune cells into the airway [109]. As a potential treatment target, TRPA1 has garnered significant attention from the pharmaceutical industry and research teams. HC-030031 is the most-studied TPRA1 antagonist. Treatment of OVA-challenged BALB/C mice with HC-030031 suppressed airway hyperreactivity and diminished the level of mucin5ac, Th2 cytokines, and leukocytes. GDC-0334 from the proline sulfonamide class inhibited TRPA1 function on sensory neurons and airway smooth muscle, directly decreasing asthmatic cough and allergic airway inflammation in different preclinical species [112]. It is reasonable to deduce that the ablation effect of bronchial thermoplasty, TLD, and cryoablation on sensory neurons, particularly of TRPA1 present on the vagus nerve, plays a significant role in

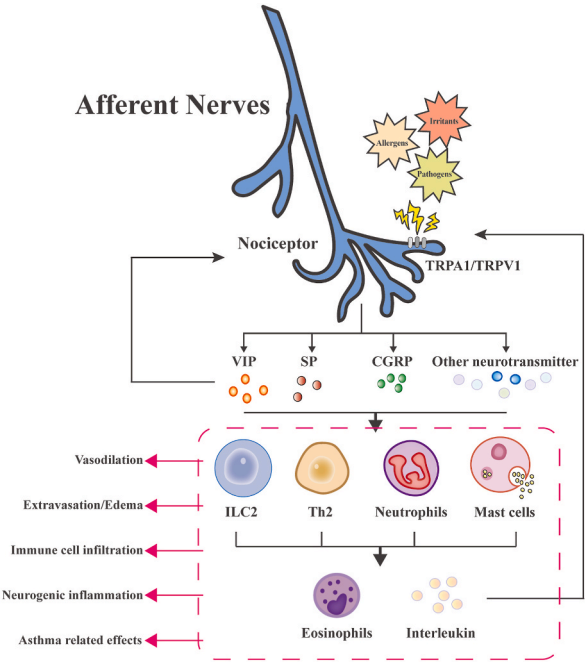

Fig. 3. Neurogenic inflammation induced by sensory neurons on afferent nerves.

suppressing asthma progression.

Now we know that when TRPA1 receives stimuli, neuro-immunity crosstalk is initiated. However, the effects of neurogenic inflammation and asthmatic symptoms rely on the indispensable intermediary transmitter. Previous studies were concerned with ACh and its interesting cholinergic anti-inflammatory reflex, while mounting evidence has transferred researchers' attention to the calcium-mediated vesicular release of several neuropeptides in asthma airways [113,114]. Thus, a discussion of related neuropeptides for asthma and neurogenic inflammation is warranted.

4.5. Relationship between neuropeptides and asthma

Neuropeptides generally refer to the endogenous active substances that exist in nerve tissue and participate in the function of the nervous system as a special kind of information substance. Drake et al. [74] found that the amount of SP is abnormally high in asthma patients, while others had noticed that the BALF in asthma patients displayed elevated neuropeptides levels, which hints at the excess activity of sensory fibers [113,114].

The stimulation of nociceptor peripheral terminals leads to the calcium-mediated vesicular release of several neuropeptides, with TRPA1 the most essential channel regulating neuropeptide release, neurogenic inflammation, and asthmatic symptoms [109]. The most studied neuropeptides within the airways are vasoactive intestinal peptide (VIP), SP, and calcitonin gene-related peptide (CGRP). Multiple immune cells, such as mast cells, macrophages, DCs, $CD4^{+}$T cells, and ILCs localize in close proximity with sensory neurons and express receptors to respond to these neuropeptides [115,116].

4.5.1. Vasoactive intestinal peptides and asthma

VIP was first isolated from the small intestine of pigs, and was simply considered as a gastrointestinal hormone. It was subsequently recognized that VIP acted as an inhibitory neuropeptide in the neuroendocrine system. The neurons of VIP are distributed in the vascular wall, tracheobronchial smooth muscle layer, bronchial mucosa mucous glands, serous glands, and ganglion cells of the lung and bronchus.

The role of VIP in asthma is debatable. Szema et al. [117] showed that *Vip* knockout mice exhibited increased airway inflammation with lymphocytes and eosinophils clustered around the bronchioles, while the levels of proinflammatory factors such as IL-5 and IL-6, and responsiveness to ACh stimulation also increased. An in vitro experimental study of human eosinophils by Dunzendorfer et al. [118] concluded that VIP inhibited eosinophil migration and produce IL-16, thus alleviating the inflammatory response. Samarasinghe et al. [119] concluded that VIP had a protective effect on airway remodeling and increased airway mucus clearance in an animal asthma model. However, others disagreed with these positive characteristics of VIP in asthma, and instead claimed that sensory neurons (such as those expressing TRPV1) secreted VIP that bound to VIP receptor type 2 (VIPR2 or VPAC2) expressed on immune cells, driving allergic inflammation. In models of OVA- or house dust mite (HDM)-induced allergic asthma, IL-5 produced by activated immune cells directly acted on Nav1.8+ neurons to induce VIP secretion. The latter then stimulated ILC2s and Th2 cells, creating a positive feedback loop that accelerated type 2 inflammation [120]. Administrating agonists of sensory neurons (such as capsaicin, a selective TRPV1 agonist) aggravates immune cell infiltration and airway inflammation. Blocking sensory neurons can effectively reverse this situation; such as by ablating $Nav1.8^{+}$ neurons or silencing them with the nociceptor-specific inhibitor QX-134 [87,121].

Whether bronchoscopy-guide IP can also achieve sensory neuron ablating effects, thus reducing VIP secretion regulating asthma, needs further investigation.

4.5.2. Substance P and asthma

SP belongs to the tachykinins. Its receptors are widely expressed in airway smooth muscle cells, endothelial cells, glandular cells [122], and mast cells. SP and capsaicin have long been regarded as potent bronchoconstrictors [123], and their activation can lead to asthma-related features such as strong contraction of airway smooth muscle, plasma leakage, and mucus secretion [124].

Levels of both SP and eosinophils in the sputum of asthma patients were increased significantly higher than sputum from healthy individuals, and their levels are closely related to the severity of the disease [125]. Hox et al. [126] found that TRPA1 activation caused airway hyperreactivity in an asthma mouse model, and also demonstrated that this phenomenon depended on a neuro-immune interactions that involved SP as a mediator and mast cell activation. Devos's team [110] confirmed this proposition by blocking TRPA1 or applying an SP receptor antagonist, and the results showed that despite the mice model becoming successfully sensitized, airway hyperreactivity did not develop. These two studies also discovered an interesting phenomenon: high concentrations of SP led to mast cell degranulation, while low concentrations of SP triggered mast cells by reducing the threshold of subsequent stimulation [127,128]. After mast cell activation, the subsequently released mediator sensitized afferent sensory fibers [129]. Early in 2007, Boot et al. [130] had already partly demonstrated inhibition of SP and neurokinin A receptors by antagonists that diminished inflammation in animal models of asthma. Unfortunately, this benefit failed to be confirmed in an asthma clinical trial.

Whether multiple inflammatory mediators act on the bare sensory nerve endings, increasing SP release through the axonal reflex, and in turn aggravating the airway inflammatory response, thus participating in the formation of airway inflammation and airway hyperresponsiveness, is worth discussing. Whether IP technology will aggravate or protect this regulation is still an unanswered question.

4.5.3. Calcitonin gene-related peptide and asthma

Calcitonin gene-related peptide (CGRP) is a potent vasodilatory substance released from peripheral endings of slowly conducting afferent neurons [131,132], and had been previously found to be a bronchodilator [133] and to effectively decrease airway

hyperreactivity [134]. Sensory neurons [135], pulmonary neuroendocrine cells [136], ILC2, and ChAT^{+} enteric neurons [137] can produce CGRP.

Some studies identified that smoke, acrolein, and crotonaldehyde directly activated TRPA1 and promoted CGRP and SP release, resulting in plasma extravasation in the airway [138,139]. However, other studies affirmed the protective effect of CGRP in asthma. Nagashima et al. found that CGRP acted on a subpopulation of ILC2s expressing the CGRP receptor complex, blocking the function of ILC2 in initiating and amplifying the inflammatory response, therefore showing an anti-inflammatory function in type 2 inflammation [140]. Wallrapp et al. [141] also demonstrated that CGRP negatively regulated alarmin-driven type 2 cytokine production and inhibited lung ILC2 proliferation, which may lead to decreased eosinophil recruitment and reduced tissue damage. Meanwhile, CGRP may also influence the adaptive immune responses in allergic asthma by inhibiting DC maturation and function. CGRP-stimulated DCs suppressed the activation and proliferation of OVA-specific T cells, while these DCs also helped stabilize allergic responses and airway inflammation when adoptively transferred to OVA-induced asthma mice [142].

Therefore, whether IP-generated heat or cold energy acting on the vagus nerve presents a growth or inhibitory effect on CGRP should become clarified, to avoid the necessary negative immune effect.

5. What Can We Deduce from the Available Evidence?

We have already quickly re-reviewed the relationship between the vagus nerve and airway neurogenic inflammation, namely, neuro-immunity in asthma. Combined with the interventional pulmonology discussion at the beginning of this review, it is not difficult for us to find that the involvement of the vagus nerve in the initiation and progression of asthma may be a multi-linked and multi-dimensional process. We now propose the following scientific hypothesis based on classical theories and findings on vagal regulation of asthma initiation and progression (Fig. 4).

Increased vagus nerve excitability undoubtedly participates in asthma pathogenesis. The vagus nerve synthesizes the neurotransmitter ACh, which is released upon excitation through efferent fibers and acts on bronchial smooth muscle, glandular cells, and a subset of inflammatory cells, causing smooth muscle contraction, glandular secretion, and inflammatory cell aggregation and activation, which accordingly leads to the typical pathophysiological changes of asthma.

In refractory asthma, the neuro-immunity molecular pathway beyond the classical understanding requires careful investigation. During the initial stage of allergen entry into the body, individuals with asthma experience denser C-fiber neuronal innervation, resulting in abnormally increased excitability [143,144]. Particularly, sensory neurons such as TRPA1 and TRPV1 exhibit a heightened responsiveness to secreted molecules from immune cells, with a lowered activation threshold [143]. These molecules can include direct irritants or those activated by IL-4, IL-5, IL-33, IL-25, and TSLP, which are released by dendritic, ILC2, and epithelial cells [109,112,145]. Activated nociceptors release neuropeptides, such as through the VIP-VPAC2 signaling pathway, which induce ILC2

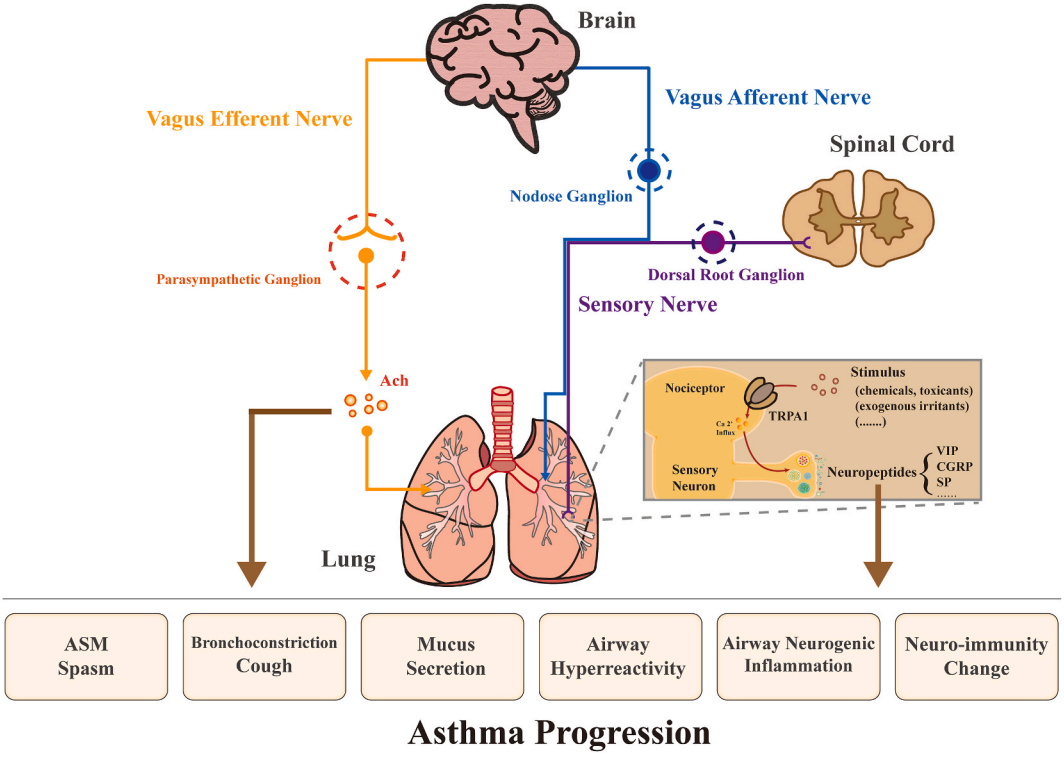

Fig. 4. Proposed schematic of neuro-immunity crosstalk in the development and progression of asthma.

activation and recruit $CD4^+$ cells for cytokine production. The downstream molecular pathway of this process is relatively complex, and currently, there is a temporary lack of authoritative and detailed research to fully elucidate it. However, some aspects of this pathway involve the activation of CGRP receptor complexes and the modulation of cAMP, phospholipase C, MAPK, and Protein kinase A signaling. Consequently, the release of Type 2 cytokines, IL-5 and IL-13, by ILC2 and Th2 cells triggers a cascade of events, including eosinophil and macrophage chemotaxis and activation, IgE secretion by B cells, goblet cell-mediated mucus production, and smooth muscle contraction. IL-5, in particular, activates nociceptors, leading to the release of VIP and other neuropeptides thereby amplifying and perpetuating a vicious cycle in the airways [87]. The culmination of these processes, known as neuro-immunity crosstalk, results in the manifestation of allergic inflammation, bronchial hyperresponsiveness, and airway remodeling, which contribute to refractory asthma.

Consideration of the pathophysiology of asthma and recent advancements in interventional pulmonology techniques, such as bronchial thermoplasty, TLD, and cryo-denervation, reveals their impact on airway tissues. Bronchial thermoplasty, in addition to reducing bronchial smooth muscle, has an impact on both nerves and neuroendocrine cells, while TLD and cryo-denervation directly target the efferent fibers of the vagus nerve, potentially impacting afferent fibers as well. These interventions demonstrate their therapeutic mechanisms' association with the blockade of neuro-immunity crosstalk. By achieving dual-ablation of both efferent and afferent fibers, they may play a crucial role in completely blocking neuro-immunity crosstalk, thereby contributing to the clinical efficacy of interventional pulmonology in treating refractory asthma.

6. What Should We Focus on in the Future?

Apparently, the relationship between the immune and nervous systems mingle to varying degrees. As neurons receive various stimuli, neurotransmitters serve as an intermediary that can directly act on immune cells, regulating the immune responses [115,146]. This regulation benefits the human body; however, excessive immune responses may lead to chronic inflammatory diseases such as asthma.

It is clear that the vagus nerve impacts the inflammation and asthmatic symptoms of the respiratory system via sophisticated regulatory interactions. How the neuro-immunity mechanism works and is maintained, and its related specific cellular interactions with afferent and efferent nerves need to be elucidated in future investigations. Therefore, future asthma management should integrate neuro-immune circuits, both local and systemic, through a more precise and comprehensive concept of airway neurogenic inflammation, in order to better create suitable approaches to control the pathology development of asthma.

First, neuropeptides, as the communication medium among sensory neurons and immune cells, can serve as the target in the regulation of neuro-immunity circuits by specifically interfering with their signaling. Shreds of evidence already showed that the entire nervous system possesses the ability to communicate with immune cells, due to the latter expressing receptors for many classes of neurotransmitters, including ACh, catecholamines, and other neuropeptides [147]. In future studies, we should identify the sources of the neuropeptides. For instance, vagal neurons, enteric neurons [148], pulmonary neuroendocrine cells [136], ILC2, and other immune cells can release CGRP during inflammation [140]. Defining the distinct contribution of individual sources of neuropeptide during type 2 inflammation and asthma progression may provide a very rewarding direction for asthma treatment. Meanwhile, we should also explore other potential neurotransmitters beyond traditional neuronal mediators that participate in this neuro-immunity process. For example, other transmitters, such as neuropeptide Y and corticotropin-releasing hormone also influence the immune response [149,150].

Second, a direct block of the vagus nerve may also be useful in this overactive response situation. The appreciable therapeutic effects of bronchial thermoplasty and its finding of decreased nerve tissue reinforces the confidence in implementing blockade of the vagus nerve with abnormally high excitability using minimally invasive interventional approaches in the treatment of chronic airway diseases such as asthma and COPD. In addition to efferent nerves and ACh secretion, TRPA1, as a target of asthma stimuli, likely promotes exposure-associated asthma exacerbations. Blocking this "signal tower" may be helpful in certain subpopulations of asthmatics through intervening in neuro-immunity processes.

Third, in addition to the above major pathways, we speculate that other pathways of the asthma neuro-immunity crosstalk are also worth consideration. Tracy et al. found in 2002 that the "cholinergic anti-inflammatory reflex" is one mechanism that modulates immune responses [151,152]. This reflex depends on ACh acting on macrophages expressing the α7 nicotinic acetylcholine receptor (α7AChR), with an inflammation suppressing effect occurring when either the vagus or splenic nerves were stimulated [153]. Further studies demonstrated that vagus nerve stimulation or an α7nicotinic agonist apparently limited tumor necrosis factor-α and high mobility group protein-1 release by macrophages, reducing an inflammatory effect. Another essential element during the process of IP treatment is the modification of interfacing tissue close to the heat or cold energy source, especially epithelial and neuroendocrine cells. In the bronchial thermoplasty study, one team demonstrated the decrease of these two cell types after surgery, while the epithelial gene changes in the process was confirmed by another research team. Thus, whether there is a connection between the two studies, and if they are potentially related to the bronchial thermoplasty therapeutic effect needs further validation. Neuroendocrine cells in epithelial tissue are recognized as another underlying control center intimately connected to sensory nerves that express TRPA1 [154]. Meanwhile, some researchers point out that pro-asthmatic neuropeptides are also released from these pulmonary neuroendocrine cells [136]. Therefore, the character of neuroendocrine cells in asthma neuro-immunity also deserves further investigation.

Moreover, communication between the intestines and lungs occurs constantly through the lymphatic and blood circulation. The gut microbiota plays a significant role in closely interacting with the mucosal immune system, employing both pro-inflammatory and regulatory signals [155]. While the thoracic duct, as the largest lymphatic vessel, facilitates the rapid encounter of the lung with mesenteric lymph, performing a crucial role in regulating the close relationship between the intestines and lungs and their associated

immune responses [156,157]. Numerous studies have provided strong evidence supporting the involvement of gut dysbiosis in the development of pulmonary complications through the concept of the gut-lung axis [157–159]. A Cross-Sectional Study [160] revealed variations in the composition of gut microbiota among different asthma patients. While study conducted on children diagnosed with asthma at preschool age also identified evidence of gut bacterial dysbiosis, further bolstering the close association between the gut-lung axis and asthma [161–163]. Furthermore, in animal models, the administration of probiotics like *Lactococcus lactis NZ9000* or *Bifidobacterium breve M-16V* has demonstrated a decrease in eosinophil infiltration, as well as a reduction in the levels of IL-4, IL-5, IL-13, and IgE, indicating effective control of lung inflammation [164,165]. Additionally, the use of *Bacteroides fragilis* appears to balance the host's systemic Th1/Th2 ratio, thereby providing protection against allergen-induced airway disorders [166]. Meanwhile, many bacteria utilize the adrenaline/noradrenaline system to regulate and propagate virulence [167], potentially influencing both the nervous and immune systems. Whether the gut-lung axis, mediated by the microbiota and probiotics, is interconnected with the lung-brain axis and may influence neuro-immunity crosstalk, also requires thoughtful consideration.

7. Conclusion

In conclusion, to our knowledge, this is the first review to summarize in detail the potential mechanism of interventional pulmonology techniques in refractory asthma treatment. According to the available evidence, we observed that neuro-immunity changes before and after intervention is a new area that we previously overlooked. Among long-term asthma patients, we further speculated that the main pathway of chronic inflammation and other pathophysiologic processes is the sensory nerve-related neurotransmitter release that forms "neuro-immunity crosstalk" and amplifies airway neurogenic inflammation. Meanwhile, other pathways, including the anti-inflammatory reflex, epithelial changes, and neuroendocrine cell responses to the intervention, also deserve attention. Future investigations on blocking abnormally excited cholinergic parasympathetic nerves and specific neuro-immunity mechanisms will greatly increase our understanding of neuroimmune interactions, and therefore finally lead us towards the elimination of asthma.

Authors' contribution

XL, SG, and FX conceived the content, drafted the manuscript, and approved the final version to be submitted. YW, XW, WG drafted the manuscript and approved the final version to be submitted. MW and JS helped in writing the manuscript and approved the final version to be submitted. KW and DL helped in writing the manuscript, revised it critically for important intellectual content, and approved the final version to be submitted. WX, and QL conceived the content, revised it critically for important intellectual content, and approved the final version to be submitted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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