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Review Article

Parasympathetic Cholinergic Dysfunction in Severe Asthma

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Abstract

Aortic dissection (AD) is a cardiovascular disease with a high mortality rate. With the rapid development of genetic testing technology, genomics can be used to predict, diagnose and treat AD. In this review, we summarize studies on AD using the genome, epigenome, transcriptome, proteome and metabolome. Multi-omics analysis can further clarify the mechanisms of AD and provide risk assessment techniques. Although related studies on the different omics of AD have been conducted, the combined analysis of multiple omics has not been studied in depth. In this paper, we will conduct an in-depth discussion of AD research using multiple omics.

Keywords: aortic dissection; genomics; epigenomics; transcriptomics; proteomics

Introduction

Asthma is a highly prevalent chronic inflammatory airway disease, affecting more than 358 million individuals globally, and is the most common chronic respiratory disease in children. It is a heterogenous airway disease with several distinct phenotypes characterized by different immunopathological pathways, clinical presentation, physiology, biomarker of allergic inflammation, and response to treatment. The hallmark of severe asthma is airway remodeling due to deposition of extracellular matrix proteins, subepithelial fibrosis, goblet cell hyperplasia and mucus hypersecretion, airway smooth muscle (ASM) cells hyperplasia and hypertrophy, and parasympathetic cholinergic dysfunction, which lead to exaggerated airway narrowing, and severe airflow limitation. T helper type 2 (Th2) cells, Th17 cells, and innate lymphoid group 2 cells (ILC2), mast cells, eosinophils, and neutrophils release proinflammatory cytokines, chemokines, adhesion molecules, and growth factors which orchestrate airway inflammation, airway hyperresponsiveness (AHR), and airway remodeling. Parasympathetic neurons in the airway plays an important role in controlling bronchomotor tone. Increased activity of cholinergic neurons contributes to AHR, and bronchoconstriction provoked by allergens, respiratory viral infection, pollutants, and chemical irritants. Neurotransmitter-driven acetylcholine from parasympathetic nerves promote airway inflammation, and remodeling, including increased ASM mass, and deposition of ECM proteins. Therefore, amplifying AHR and remodeling, leading to severe bronchoconstriction, and persistent asthma.

The standard of care treatment, and biologics do not ameliorate airway remodeling, especially due to ASM hyperplasia and hypertrophy, and parasympathetic cholinergic dysfunction. The therapeutic strategies for this phenotype of cholinergic-driven asthma, should include add-on treatment with long-acting anticholinergic antagonists, or bronchial thermoplasty to remove excessive ASM mass, and the hyperreactive cholinergic nerves.

The physiological effects of efferent nerves in the airways are mainly mediated by the postganglionic parasympathetic cholinergic neurons that cause airway smooth muscle (ASM) cell to contract, and the non-adrenergic and non-cholinergic (NANC) fibres which induces bronchodilatation via nitric oxide (NO), and vasoactive intestinal peptide (VIP) [1]

The principal neurotransmitter secreted at the neuromuscular junction by parasympathetic nerves is acetylcholine, which binds to airway muscarinic receptors to trigger smooth muscle contraction, and mucus secretion [2, 3]. There are five identified muscarinic receptors that belong to the G-protein-coupled receptor family [4]. However, only M1, M2, and M3 receptors have been shown to play major roles in airway physiology, and in diseases, such as asthma and COPD [5].

Parasympathetic neurons in the airway play an important role in controlling bronchomotor tone. Increased activity of cholinergic neurons contributes to airway hyperresponsiveness (AHR), and bronchoconstriction provoked by allergens, respiratory viral infections, pollutants, and chemical irritants [6-8]. Additionally, the parasympathetic cholinergic nervous system plays a key role in inducing respiratory symptoms experienced by asthmatic patients, such as cough, dyspnoea, and mucus hypersecretion [6,9]. Cholinergic nerve-mediated obstruction

of the airways is increased in asthma and COPD [10,11], and contributes to persistent airflow limitation in patients with asthma [12].

Recently, increased branching and lengthening of sensory nerves in the airway has been demonstrated to occur in asthmatic patients, and correlate with disease severity [13]. This indicates that changes in neuronal architecture may contribute to persistent AHR and remodeling [7]. Additionally, acute sensitization of sensory neurons through changes in excitation, activation threshold, or transmission have been reported in patients with asthma [6].

Neurotransmitter driven acetylcholine from parasympathetic nerves may promote airway inflammation, and remodeling, including deposition of ECM proteins, goblet cell hyperplasia and mucus hypersecretion, increased ASM hypertrophy [2, 14-17]. Furthermore, cholinergic stimulation may has a long-term effects on target cells, such as ASM cells, and mast cells, by inducing secretion of cytokines, chemokines, growth factors, and even ECM proteins [18]. Therefore, orchestrating airway inflammation, AHR, and remodeling. Airway remodeling leads to narrowing of the airway lumen and increase in airflow resistance, and fixed airflow obstruction. Consequently, it leads to severe, and difficult to control asthma with the standard of care.

The mechanisms of neuronal sprouting in asthmatic airways, and cholinergic hyperreactivity is complex. Neurotrophins are produced by neurons including astrocytes in the brain, ASM cells, epithelial cells, and many structures that the nerves innervate. They foster the production of proteins associated with central and peripheral neuronal development, growth, and survival. There are several neurotrophins, such as nerve growth factor (NGF), neurotrophin 3 (NT-3), and NT-4/5, but the most important neurotrophin in the airways is brain-derived neurotrophic factor (BDNF) [19]. BDNF consists of three known protein isoforms of different molecular weight (precursor, truncated, and mature BGNF). There are four high-affinity tropomycin-related kinase (Trk) receptors (TrkA, TrkC, TrkB, and p 750, and mature (cleaved) BDNF signaling is via TrkB [20]. Brain-derived neurotrophic factor, and its receptor (TrkB) receptor play an important role in the regulation of the bronchomotor tone [20,21]. TrkB signaling play an important role in the development of increased cholinergic nerve density after chronic allergen exposure in mice [7]. Furthermore, BDNF/TrkB signaling has been shown to contribute to AHR in animal model of asthma [22,23]. BDNF contributes to the production and deposition of ECM proteins, and subepithelial fibrosis, thereby promoting airway remodeling [24].

The expression of BDNF is increased in the lungs after allergen challenge in murine model of asthma [25]. Similarly, BDNF expression is increased in sputum and bronchial biopsies in asthmatic patients which correlates with diseases severity [19]. Furthermore, bronchial biopsies from asthmatic patients show an increase in cholinergic fibres and increase TRkB gene expression in human lung tissue, and single-nucleotide polymorphisms (SNPs) in the NTRK2 (TrkB), and brain-derived neutrophic factor (BDNF) genes linked to asthma [7].

Parasympathetic cholinergic neoplasticity and dysfunction, and over expression of BDNF play an important role in the pathogenesis of severe, uncontrolled asthma. Treatment of patients with this phenotype of asthma requires targeting the acetylcholine and its M3 receptors with long-acting antimuscarinic antagonists, or ablation of the hypertrophied ASM mass together with the hyperreactive cholinergic nerves.

Treatment:

Approximately 3.6-10% of patients with asthma have severe refractory disease, which is uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS), and long-acting β2-agonists (LABA) [26-28]. Additionally, about 10-25% of patients at step 3 or higher in the Global Initiative for Asthma [29] have an exacerbation with 1 year [29,30]. Treatment of severe asthma, particularly associated with airway remodeling, ASM hyperplasia and hypertrophy, accompanied by parasympathetic dysfunction is challenging.

Long-acting antimuscarinic antagonists (LAMA), such as tiotropium are effective in reducing asthma symptoms. They improve asthma control, health-related quality of life (HRQoL), and lung function, and reduce exacerbation rates [31-33]. LAMA have a long, and impressive pharmacokinetic and pharmacodynamic history in the management of asthma, COPD. The previous orphanage LAMAs have now resumed a pivotal role in the treatment of chronic obstructive airway diseases.

The Global Initiative for Asthma (GINA) strategy document [29], and the National Asthma Education and Prevention Program guideline [30], have recommended initiation of tiotropium at step 4 or 5 before oral corticosteroids and biologics. In addition, the European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force recommends tiotropium as add-on to ICS/LABA in patients with severe asthma regardless of phenotype [34].

There are now several LAMAs that have been approved or are in clinical development for the management of asthma and COPD. Most impressive, some of the LAMAs are administered as a single-inhaler triple combination with a LABA and ICS [35-37] **(**Table 1). Moreover, in uncontrolled asthma, addition of a long-acting muscarinic antagonist to ICS plus LABA therapy has been reported to significantly improve asthma symptoms, and lung function [35-37[, and significantly decrease exacerbations in the TRIMAN study [35,36], but non-significantly reduced exacerbations in the TRIGGER and CAPTAIN trials, compared with ICS/LABA single-inhaler double therapy [37]. Single-inhaler ICS/LABA/LAMA (SITT) formulations are an effective treatment option with a favorable safety profile, and are convenient for the patients. Noteworthy, SITT improves patient compliance because they have to use only one inhaler device. According to the GINA guidelines, add-on LAMA or single-inhaler triple should be initiates at step 4 or 5 before oral corticosteroid, biologics, or bronchial thermoplasty. Table 1 shows the single inhaler triple therapy drug combinations.

Bronchial thermoplasty (BT) is a bronchoscope therapeutic intervention which uses a special Alair™ catheter (Bronchial Thermoplasty System, Natick, MA, USA) [38] to remove excessive ASM mass, ECM proteins, subepithelial fibrosis, submucous glands, and nerve endings [39,40]. Bronchial thermoplasty should be offered to carefully selected patients in specialized centers by experienced pulmonologists or bronchoscopists. It is a safe procedure and has long-term benefit in reducing asthma symptoms, and exacerbations, and in improving the HRQoL, and lung function [40-46]. It has been demonstrated to allow patients to taper corticosteroids.

Table 1:

Single-inhaler dual therapy - LABA/LAMA
Formoterol – Glycopyrrolate
Formoterol – Aclidinium
Vilaterol – Umclidinium
Olodaterol – Tiotropium
Single-inhaler dual therapy - LABA/ICS
Albeterol - Budesonide
Salmeterol – Fluticasone propionate
Formoterol – Beclomethasone dipropionate
Formeterol – Budesonide
Formeterol – Mometasone
Vilanterol – Fluticasone
Indacerol – Mometasone
Single-inhaler triple therapy - LABA/LAMA/ICS
Beclomethasone dipropionate – Formeterol – Glycopyrronium

Budesonide – formoterol – Gylcopyrronium

Fluticasone furoate – Vilanterol – Umeclidinium

TABLE 1: Single-inhaler dual, and triple therapy combinations for the treatment of severe asthma

Conclusion:

Severe asthma is characterized by airway hyperresponsiveness, and remodeling. Airway remodeling is a complex structural change in which there is subepithelial fibrosis, goblet cell hypertrophy and mucus hypersecretion, ASM hyperplasia and hypertrophy. Additionally, there is neovascularization, and parasympathetic cholinergic dysfunction. Treatment of cholinergic-driven severe asthma requires addition of a LAMA or SITT. Patients with severe asthma should be offered the opportunity to undergo bronchial thermoplasty. BT is safe in experienced hands in reducing asthma exacerbations, improving asthma control, lung function, and HRQoL.

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