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Omics techniques reveal the pathogenesis of microbial communities in asthma

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Abstract. The presence of airway hyperresponsiveness in asthma provides the basis for constriction in bronchus response to a variety of stimuli, leading to limited airflow, dyspnea, wheezing, and chest tightness, threatening patients' lives. Statistics have shown that asthma is more prevalent in the adolescents and children than in the adults, suggesting that early ecological dysregulation of the gut and airway microbiome contributes to the occurrence of asthma, especially in the preschool years' children. With the development of high-throughput sequence technologies such as genomics, it has become possible to study the association of pathophysiological processes of allergic reactions and ecological dysregulation using the multi-omics techniques. In this review, the author first briefly introduces the classification of asthma, summarizes the pathogenesis of microorganisms in asthma, providing a new direction and ideas for the research of the pathogenesis, diagnosis, and treatment of asthma.

Keywords: Asthma, Omics, Microbiome, High throughput sequencing

1. Introduction

As a relatively common bronchial disease, hyperresponsiveness in airway is an important clinical feature of asthma, serving as the foundation for bronchoconstriction in response to a range of stimuli, which can result in a number of life-threatening symptoms include dyspnea, wheezing, chest tightness, and airflow restriction [1]. Statistics have shown that asthma is more prevalent in the adolescent and child population than in the adult. And it is well documented that early ecological dysregulation of the gut or airway microbiome predisposes children to follow the trajectory of asthma [2]. This is because viral and bacterial infestation can contribute to wheezing, especially in the preschool years, and infestation of the airways by *rhinoviruses* (RVs), *respiratory syncytial viruses*, and *parainfluenza viruses* is a common contributing factor in the development of wheezing and acute asthma, and the overabundance of certain bacteria has been shown to be associated with episodes of wheezing, such as *Haemophilus influenzae*. The primary cause of early airway structural changes, which may ultimately result in the early onset and exacerbation of airway remodeling, is genetic defects or variants that sensitize airway epithelial cells to environmental stimuli. Recurrent viral infections can also induce and prolong airway hyperresponsiveness.

The early sign of asthma often manifests as wheezing. While common respiratory infections are known to stimulate type 2 inflammation, allergic sensitization usually precedes wheezing triggered by infections. Interestingly, most children who suffer from wheezing due to viral infections in their early

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childhood and preschool years do not progress to develop chronic asthma later in life, suggesting that further exploration is needed regarding the association and mechanisms between infections and asthma development. The high-throughput genomics technologies has become possible to study the biochemistry and pathophysiology behind allergic reactions, presenting application in clinic through identification of new markers and analysis of enrichment functions [3]. In this paper, the author first briefly introduces the classification of asthma and summarizes the pathogenesis of microorganisms in asthma, focusing on the analysis of new advances in high throughput sequencing technology in the pathogenesis and diagnosis of asthma in recent years, providing a new direction and ideas for the pathogenesis of asthma and diagnosis and treatment of asthma research.

2. Classification and phenotypic characteristics of asthma

The asthma is classified by the clinical features, such as the recurrent episodes of wheezing with shortness of breath, which are associated with exposure to allergens, cold air, exercise, etc., named as typical asthma. In contrast to typical asthma, the main manifestations of atypical asthma are that the coughing and chest tightness often occur at early morning or mid-night, strenuous exercise, or exposure to cold air can be triggered by the symptoms of the aggravation of the asthma. According to the triggered factors, the asthma can be divided into different classification from inducing factors such as allergy, exercise, and drug. Allergic asthma occurs in the allergic population, mainly triggered by allergic substances, who is accompanied by allergic rhinitis and other allergic diseases with symptoms of sneezing, runny nose, cough and chest tightness and other symptoms. Exercise asthma is mainly triggered by exercise and the onset of this type of asthma is usually rapid. Pharmacologic asthma is mainly caused by the intake of aspirin enteric-coated tablets or beta-blockers, which is usually characterized by recurrent episodes of shortness of breath, chest tightness and cough. Occupational asthma is mainly caused by frequent exposure to synthetic fibers or adhesives at work, with its main symptoms of chest tightness and coughing during or after hours of work, in addition to rhinitis or conjunctivitis, which are relieved after leaving the workplace.

3. Omics techniques in asthma

3.1. Omics techniques reveal changes in asthma pathology

MicroRNA belongs to non-coding RNA with 18-22 nucleotides that plays a regulatory role in inflammatory diseases. Anshul Tiwari's group conducted a study sequencing small RNAs from mild-to-moderate asthma children (n=398) using the baseline data from seasonal asthma controls. They assessed the impact of allergen sensitization status determined using baseline skin prick tests. Initially, they utilized DESeq2 to identify seasonal differences in miRNA expression, followed by regression analysis to investigate associations between allergens sensitization and differentially expressed miRNAs (DE miRs), eventually revealed 52 miRNAs out of 81 DE miRNAs. Subsequently, they delved into the association between these miRNAs and seasonal allergen sensitization using skin prick tests, finding two miRNAs showed significant associations with allergic symptoms among identifying 26 miRNAs. Interestingly, let-7d-3p exhibited a potentially protective effect against asthma, while miR-328-3p was detrimental to asthma of mulberry trees. Furthermore, the authors conducted an enrichment analysis of target genes regulated by DE miRNAs, revealing significant enrichment in pathways such as Rap1, Ras, and MAPK signaling pathways according to DAVID analysis [4]. This suggests that miRNAs may be involved in asthma by influencing the above signaling pathways.

Regarding the relationship between type 2 biomarkers and the development of asthma, one research group performed a high-throughput transcriptome analysis using 738 whole blood samples from patients suffering from severe asthma with high/low T2 biomarkers. A large amount of RNA-seq data was obtained from 301 participants' blood samples, and unsupervised cluster analysis was first performed to identify 2 clusters. Because patients with high T2 biomarkers had low blood eosinophil counts, were more symptomatic, and were more likely to receive oral corticosteroid (OCS) therapy.

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Therefore, the authors identified 2960 and 4162 DEGs using the principle of OCS stratification in differential gene expression analysis. 2960 genes were adjusted by subtracting the OCS signature genes, and 627 genes remained differential involving the biosynthesis of polylidene-bisphosphate oligosaccharides and assembly of the RNA polymerase I complex. However, no stable DEGs were associated with patients with low T2 biomarkers after a trial in clinic, whereas many DEGs were associated with elevated T2 biomarkers, and 15 DEGs among them increased independent of patient symptoms [5].

In addition, high-throughput related sequencing analysis contribute to identify and classify asthma, such as the method of Tape-strips, which is a minimally invasive method of skin sampling that can be used to evaluate a wide range of skin disorders used for asthma detection. Del Duca E et al. collected three groups samples of moderately allergic asthmatic (MAA) children, severe allergic asthmatic (SAA) children and healthy group controls (HC). Subsequently, 1113 and 2117 DEGs were identified in MAA and SAA patients, separately. To distinguish asthma patients from HC using transcriptomic biomarkers, these DEGs were associated with asthma-related symptoms, such as exacerbation rate, lung function of FEV1. Significant downregulation of epidermal transcriptome biomarkers were identification including cell adhesion, terminal differentiation, and lipid biosynthesis/metabolism. The Th1/IFN-γ pathway were enrichment through gene set variant analysis. The genes of G protein-coupled receptors, TGF-β/ErbB signaling-associated proteins up-regulated in both MAA and SAA patients. Skin transcriptome biomarkers were associated with annualized exacerbation rates and lung function parameters, such as TSSC4-FAM212B discriminating asthma from HC with 100% accuracy [6].

3.2. The microorganisms contribute to the pathogenesis of asthma

Microbial homeostasis plays a key role in asthma development although the effects of indoor metabolites on health have not been understand clearly. Yu Sun's group collected classroom dust from 24 schools in three locations of distant areas, and performed culture-independent high-throughput microbiome and non-targeted metabolomic/chemical analyses through surveying of a 1290 asthma students. Results revealed significant differences in the prevalence of wheezing between schools at each study center, which could be explained by individual characteristics and air pollutants. Large-scale microbial variability was observed among the three centers with different potentially protective organisms through identification 2633 metabolites and chemicals. Many metabolites were enriched in the low-surge colonies, such as their derivatives. Neural network analyses showed that indole derivatives coexisted with potentially protective microbial taxa, such as *Actinobacillus sphaericus*, *Fischerella sphaericus*, and *Tropezia*, suggesting that these microorganisms may influence health status through the release of indole metabolites. A number of synthetic chemicals are enriched in high wheezing schools, suggesting that they have an aggravating effect on asthma [7].

Microorganisms have an important impact on asthma development, but the impact of fungi on asthma is still poorly understood. Samuel J. Cochran and his team set out to investigate the correlation between fungal diversity and the prevalence of asthma within neighborhoods. Their objectives were to examine household fungal diversity and identify particular fungal species, contributing valuable insights into the environmental factors influencing respiratory health in urban settings. First, author recruited 7-8 year old (n = 347) children living in neighborhoods with high (11-18%) and low (3-9%) asthma prevalence. Subsequently, the authors sequenced fungal communities in floor dust, found that the building type and the presence of bedroom carpet influenced the prevalence and diversity of neighborhood asthma. Additionally, a subgroup of 140 asthmatic children underwent follow-up until 10-11 years of age to assess asthma persistence. Among the 7-8-year-old asthmatic children, it was observed that *Shannon's* fungal diversity showed a negative correlation with frequent symptoms of asthma at that age and asthma persistence into later years. Despite analyzing individual fungal species, no significant associations with asthma outcomes were noted after adjusting for false discovery rates [8]. This suggests that fungal-induced asthma is not dominated by a particular group of fungi, but rather a combination of various fungal interactions with the environment and the organism.

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In addition, the Leonardos Mageiros research group summarizes the results of recent studies on the relationship between viruses and asthma, as described above, viruses are strongly associated with the asthma progression, but the impact of virus-host interactions on asthma is still unclear, so the objective of this paper is to investigate the possibility that allergic diseases may be influenced by interaction between virus and host. However, little studies investigating the virome suggests that future studies will require prospective replicated sampling designs to reveal the impact of the virome on asthma development and its interactions with the microbiome and immunity [9]. The application of omics techniques in asthma are listed in Table 1.

Table 1. The omics data in asthma.

Omics data in asthma	Examples
Prediction	The fungal diversity is negatively correlated with the prevalence of asthma [9].
Diagnosis	The TSSC4-FAM212B was able to discriminate asthma from HC [6].
Pathogenesis	Many DEGs were associated with elevated T2 biomarkers [5].
Treatment	The miR-let-7d-3p is a candidate in therapeutic asthma, whereas miR-328-3p exacerbates in allergic asthma to mulberry trees [4].

4. Summary and prospect

High-throughput sequencing and its related analytical techniques contribute to identify new genes responsible for asthma pathogenesis and reveal the mechanisms of microbial roles in asthma development and disease progression. For example, researchers have found that miR-328-3p are significantly associated with symptoms of seasonal asthma. In addition, transcriptome analysis by collecting microorganisms in large samples from multi-regions and multi-centers can provide new insights into the prediction, prevention and precise control of asthma. Moreover, in recent years, high-throughput sequencing has further explained the effect of fungal diversity on asthma occurrence, suggesting that the diversity of fungal species can reduce the incidence of asthma.

With the development of omics technologies, it is possible in the future to find more precise ways to reveal the pathological changes in asthma, and to show the influence and mechanisms of microorganisms in asthma by continuously optimizing clustering and sequencing techniques. In the urban environment, the incidence of asthma is higher in the locations of lower fungal diversity. Future needs to utilize the methods and approaches of prospective studies to reveal the roles and mechanisms of viral groups in causing allergic diseases.

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