

Understanding the role of airway microbiome

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Asthma is a heterogeneous chronic airway diseases include various phenotypes and endotypes. Once airway of healthy individuals was considered as sterile. However, it is known that airway is full of commensal and symbiotic microorganisms, 'microbiome'. Currently, microbiome has emerged as a missing piece which can explain the pathogenesis of diverse chronic diseases. Microbiome research in asthma has been focused on the association between characteristics of airway microbiome and the development, severity, and treatment response of asthma. Proteobacteria is found to be increased in asthmatic airways but its role in the development and exacerbation of asthma is not clearly validated. More intensive research focused on the functional aspect of microbiome related with inception and exacerbation of asthma according to subtypes based on pathophysiological features are needed in order to uncover the pathogenesis of asthma.

1. Introduction

Asthma is a chronic allergic airway disease having genetic predisposition. However, despite completion of human genome project and discovery of diverse candidate genes identified by the genome-wide association study (GLS) and genome-wide association study (GWAS),¹⁾ the pathophysiology of asthma is still unclear and difficult to attain a complete control. Recently, the concept that asthma is not a single disease but a disease entity presenting various phenotypes and endotypes with similar clinical characteristics such as airway hyperresponsiveness and chronic airway inflammation. However, there is no established biomarker or targeted therapeutic option based on pathophysiology.^{2,3)}

Microbiome refers to a collection of all microorganisms such as bacteria, viruses, and fungi those are mainly present in human epithelial cells such as human intestine, respiratory tract, skin, and genitalia. Recently, human microbiome is being expected to provide a clue which will enable us to understand and overcome various chronic diseases. Although airways were believed to be sterile in normal condition until

recently, microbiome studies revealed that airways are full of diverse bacteria even in the absence of diseases. As a result, enormous attention has been paid to the roles of microbiota in the development and maturation of airway.⁴⁾ Especially, the effects of human microbiome on the maturation of immune system during early years and the development of chronic respiratory and allergic diseases according to microbiome composition have been investigated.⁵⁻⁸⁾

2. Hygiene hypothesis and microbiome

In late 1980s, 'hygiene hypothesis' was introduced to explain the increasing trend of allergic disorders in modern society. Hygiene hypothesis was based on the assumption that the reduced infection risk in early years with help of antibiotics use, smaller size of family, and birth order may affect the immune maturation toward development of allergy.⁹⁻¹¹⁾ However, with further investigations, hygiene hypothesis exposed its limitation to fully explain the allergy epidemic and other contributing factors were suggested.¹²⁾

Several factors such as recent improvements in personal hygiene, disruption of the microbial environment, increased use of antibiotics seems to contribute to the dysregulation of homeostasis between humans and inner body microbes and evidences are growing recently. The 'loss of old friend hypothesis' means changes of homeostasis result in the decrease of beneficial normal resident flora and eventually contributed to the increase of allergic disease.

3. Asthma and gut microbiota

Gut microbiome is the most active target in microbiome studies. The microbiome of the oral cavity, skin, and gastrointestinal tract of a newborn is affected by the types of delivery and the risk of allergic sensitization is significantly higher in newborns born through cesarean section than compared to those born vaginally.¹³⁾ *Lactobacillus* in the vagina was found predominantly in the newborns born vaginally, whereas newborns born through cesarean section were dominated by microorganisms in the skin such as *Staphylococcus* and *Streptococcus*.¹⁴⁾ *Clostridium difficile* is predominantly present in the intestines of newborn born and showed association with the later development of asthma and atopy.¹⁵⁾

After birth, intestinal microbiomes are affected by diet and antibiotic use and become similar to adult microbiome patterns over the years.¹⁶⁾ During the process, the use of antibiotics in early life affect microbiome composition and the development of asthma in childhood.^{8,17)} The intestinal microbiome also affect allergic sensitization.¹⁸⁾ Epidemiologic studies showed the association between decreases in intestinal bacterial diversity and increased allergic sensitization¹⁹⁾ and an animal study also revealed similar association.²⁰⁾ Gut microbiome is involved in the defense mechanism of the host against respiratory infections²¹⁾ and it can be controlled by the intake of specific strains.²²⁾

Gut microbiota can regulate the airway mucosal response through the metabolites. In the high-fiber-fed rats, the proportion of *Bacteroidaceae* and *Bifidobacteriaceae* increased in the intestines and this dietary change decreased expression of IL-4, 5, 13, 17A and sensitization to house dust mites.²³⁾ These findings suggested that manipulation of gut microbiota can be applied for the prevention and treatment of asthma.

4. Asthma and airway microbiota

Recently, a study about the effect of airway microbiome on asthma inception, phenotype, immune differentiation, and allergy sensitization have been performed.²⁴⁾ Many studies have shown increase of *Proteobacteria* in asthmatic patients.^{5,6,25-27)} Species such as *Comamonadaceae*, *Sphingomonadaceae*, and *Oxalobacteraceae* belonging to *Proteobacteria* have a strong association with bronchial hyperresponsiveness.²⁷⁾ In addition, asthma phenotypes, including corticosteroid resistance, decreased lung function, and increased sputum neutrophil count, were also associated with bronchial microbiome changes, especially increase of *Haemophilus parainfluenza*, a type of *Proteobacteria*.^{7,26)} There is a study which examined the direct interaction of asthma and microbiome. The presence of *Moraxella catarrhalis* was associated with an increase in specific gene expression in asthmatics, suggesting that certain bacteria may interact with the host.²⁸⁾

Early studies on the relationship between asthma and airway microbiome were conducted by using bronchial specimens from bronchoscopy, but there are many studies carried out with induced sputum, relatively noninvasive and easy to collect specimen in larger number of patients. Like studies using bronchoscopy, asthmatic patients had significantly higher proportion of *Proteobacteria* but lower proportion of *Actinobacteria* and *Firmicutes* in the study using induced sputum.²⁵⁾ Other study using induced sputum also replicated the difference in microbiome composition according to the asthma phenotype reported in the study using bronchoscopic specimen.²⁹⁾

5. Conclusion

To date, there have been many reports of epidemiologic associations with asthma-related microbiome studies, but recent studies have reported the relationship between microbiome and asthma phenotypes or response to asthma treatment. However, there is still a lot of uncertainty to conclude the role of microbiome in the pathogenesis of asthma. More in-depth research is needed to clarify the role of airway microbiome in asthma and functional analysis rather than association study is required in order to explore a new therapeutic target.

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