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Editorial

Does the Difference in Microbial Patterns in the Airways Induce Distinct Endotypes of Asthma?

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▸ See the article "Relationship of Microbial Profile With Airway Immune Response in Eosinophilic or Neutrophilic Inflammation of Asthmatics" in volume 12 on page 412.

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Bronchial asthma is a very complicated and heterogeneous disease that affects about 300 million people worldwide.[1] It has been classified into several phenotypes according to various inflammatory mechanisms. In addition to type 2/ eosinophilic inflammation, non-type 2 inflammation (including neutrophilic, mixed granulocytic, and paucigranulocytic types) were reported.[2,3] Although there have been many studies on eosinophilic airway inflammation,[4-6] there are still limited studies on non-type 2 inflammation which responds less to current treatment, leading to severe asthma.[7-9]

Recently, there has been growing interest in inflammation of the airway epithelial barrier and microbiome-associated airway inflammation.[10] Many studies on the development of future allergic diseases following viral exposure in the early childhood stage and the introduction of allergens into the airway wall and the existing hygiene theory are well known.[11-13] It has been less than a few years since the concept that the lower airway of a normal person is sterile. It is now clear that human lungs contain a variety of common microbes, especially bacteria, that can show considerable heterogeneity between individuals and between lung areas.[14,15] The association between asthma inflammatory phenotypes and airway microbiology is very complex and bidirectional. Huffnagle et al.[16] suggested that we need to focus on whether the altered microbiome of the lung initiates and enhances chronic inflammation or is a simple marker of injury and inflammation whether the lung microbiome actually modifies the progression of chronic inflammation by the treatment that modulates them, and whether other molecules (metabolites) generated from inflammatory processes promote cross-kingdom signaling and augmentation of virulence.

In the current issue of the *Allergy, Asthma & Immunology Research*, Son et al.[17] attempted to assess the association between microbial profiles in the induced sputum and inflammatory characteristics in asthmatic airways. They hypothesized that the interaction between inflammatory cells and the microbiome in the asthmatic airways may be bidirectional and tested the hypothesis by assessing the microbiome, inflammatory cells and cytokine profiles. They reported larger operational taxonomic units in the mixed and neutrophilic inflammation groups than in the paucigranulocytic inflammation group. They also analyzed the induced sputum from 4 types of asthma at the species level. Furthermore, they reported different correlations between cytokines and the percentage of eosinophils according to IL-5

and IL-13 concentrations. The notable part of this study is the results of the paucigranulocytic group. Indeed, paucigranulocytic asthma is a newly proposed subtype of asthma, of which underlying mechanism has largely been unknown.[18] Unfortunately, the comparison with normal people is not done in this study. However, the microbial diversity of asthma has been known to decrease compared to normal subjects.[19] Among asthmatics, the microbiome diversity was reported to be higher in eosinopihilic asthma than in non-eosinophilic asthma.[19] According to the definition of inflammatory patterns in the asthmatic airways, non-eosinophilic asthma includes both neutophilic and paucigranulocytic asthma. It has also been reported that the bacterial burden in neutrophilic asthma was higher than that of non-neutrophilic asthma.[15] Taken together, these reports suggest that microbial diversity may be lower in paucigranulocytic asthma than in eosinophilic and neutropihilic asthma, which is in accordance with this observation. However, this study showed neither direct nor indirect evidence for the linkage between eosinophilic inflammation and the bacteria species identified. Molecular and functional analyses of these species would be essential for understanding the association between microbiome and airway inflammation. This still remains to be explained and studied further. However, it seems likely that this study of 4 phenotypesprovides new insight into asthma pathogenesis.

A gold standard to evaluate microbiome in the airways has not yet been established, especially about the type of samples. It is debatable which sample accurately reflects the microbial environment of the lower airway. In addition, Pang et al.[20] argued that induced sputum may not be a valid surrogate for the microbiome assessment of the lower airways in all individuals because many bacteria in the samples were not recognized by the standard method amplifying the V3-V4 16S rRNA gene region, although this technical limitation has been overcome by the introduction of the next generation sequencing (NGS). Nevertheless, Son's research[17] is the first to evaluate the relationship between airway microbiota and inflammatory profiles, which is valuable in clinical and therapeutic implications.

In conclusion, the difference in microbial patterns in the airways may induce distinct endotypes of asthma, which is responsible for neutrophilic or eosinophilic inflammation in asthma. This study may contribute to understanding the relationship between microbiome and the type of airway inflammation. It may also provide fundamental knowledge to control inflammation in asthma by targeting candidate microbes and to develop novel drugs and treatment strategies for uncontrolled asthma. Although inter-correlations between microbiome, inflammation, and cytokines were observed, the cause-and-effect relationship among them was not clarified. Further studies in a large number of data on the mechanism underlying the inter-correlation are needed to clarify the precise role of microbiome in allergic inflammation and to develop a novel therapy targeting the microbiome.

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