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Editorial

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Does the Serum Tell Us Something About the Host-Microbial Relations in Allergic Diseases?

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▸ See the article "Diagnostic Models for Atopic Dermatitis Based on Serum Microbial Extracellular Vesicle Metagenomic Analysis: A Pilot Study" in volume 12 on page 792.

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A plethora of researches over the past decades has revealed that micro-organisms play critical roles in a variety of diseases by dynamically interacting with hosts and their immune systems.[1] Particularly, clinical associations between microbial dysbiosis and allergic diseases such as atopic dermatitis (AD), allergic rhinitis, and asthma have been repeatedly reported.[2,3] The underlying mechanisms of dysbiosis found in patients with allergic diseases are yet largely unknown, and the precise role of dysbiosis in their pathophysiology is just beginning to be defined; nevertheless, it is quite clear that different patterns of microbiota exist in the patients with allergic diseases and are closely associated with disease development. This rapidly developing research area is believed to be promising, and defining the host-microbial interactions is an exciting task. At the same time, in order to achieve valuable advances in this field, it is pivotal for researchers to pay special attention to the currently available tools for microbiome investigation and acknowledge their limitations.

Metagenomic analysis is a culture-independent method using human samples for 16s rDNA sequencing to identify and quantify the microbiota in different body sites. This method became a standard tool for understanding the features of the human microbiome as a whole owing to technological advancements such as next-generation sequencing. Nevertheless, as the field of metagenomics is a relatively new area, its results should be carefully interpreted in computational and statistical assessments due to the variability in study cohorts and designs. Possible shortcomings of bioinformatics should also be considered. Given that employing metagenomics generates huge amounts of data and demands elaborative and complicated computational analysis, investigators should keep in mind the pros and cons, values, and clinical meaning of the results obtained from metagenomic data analysis.[4]

Furthermore, the collection site of human biologic samples for metagenomics is also a crucial factor that researchers should focus on. In order to elucidate the role of certain microbiota in a given disease, biologic samples are usually obtained from the principal anatomic site in which the disease develops. Accordingly, the major anatomic sites of interest for AD and asthma are the skin and the airways, respectively. Indeed, multiple studies have reported significantly altered microbial patterns in the skin lesions of patients with AD.[5,6] Meanwhile, an extensive amount of research has been performed on the human gut microbiota and its role in diseases by evaluating its interaction with the immune

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system,[7,8] and demonstrated that the gut microbiota has a great impact on the host immune function. As such, the features of the gut microbiota in AD patients have been analyzed and were found to have significantly different patterns compared with those in healthy controls.[9,10] What, then, is the role of the serum as a source of human biologic sample for metagenomics analysis?

In the current issue of *Allergy, Asthma & Immunology Research*, Yang et al.[11] assessed the microbial profiles of AD patients by analyzing their serum extracellular vesicles (EVs), which are nanometer-sized particles that function as intercellular signaling mediators. The authors found different diversities in the metagenomic analysis for serum EVs between controls and AD patients, and suggested serum EVs as a potential source of biomarkers in AD. Blood is easy to obtain and is able to reflect systemic condition and may thus be a practical diagnostic tool in AD. Furthermore, utilizing serum EV metagenome has proven to be advantageous as it provides an excellent tool for demonstrating the systemic effects of the total microbial community residing in anatomic sites including the gut, skin, and even the respiratory tract. In addition, using serum instead of skin lesions in AD may confer additional benefits, because the skin is directly affected by the environment and the samples are more likely to be contaminated during collection as the authors suggested.[11] Nevertheless, the clinical meaning and value of serum EV metagenomic analysis should be verified by analyzing and comparing the serum and skin samples and by comprehensive interpretation of the results based on the precise clinical features of AD. For metagenomic analysis using different types of biologic samples, using serum EVs for identifying the patterns of microbiota is likely to be not an issue of methodologic superiority, but an issue of integrating our understandings of the human microbiome and diseases.

Finally, Yang et al.[11] suggest that serum microbial EVs have a potential for use as novel biomarkers for the diagnosis of AD. Considering that AD is a complex and heterogeneous disease, the diagnostic value of serum EVs should be evaluated in well-defined AD subtypes. Additionally, most of the analytic tools in metagenomics can only suggest an association between a certain disease and a pattern of microbiota, not a cause thereof. In order to elicit a valuable meaning in the therapeutic aspect based on the results of metagenomic research on microbiota, investigators need to conduct beyond mere clinical association studies. To obtain further improved value through serum EV analysis, well-designed experiments and clinical studies should be carried out in the near future to elucidate the cause-and-effect relationship between the microbiome and the pathogenesis of AD and other allergic diseases.

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