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Editorial

Urine Microbial Extracellular Vesicles Can Be Potential and Novel Biomarkers for Allergic Diseases

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▸ See the article "Bacterial Microbiota-derived Extracellular Vesicles in Children With Allergic Airway Diseases: Compositional and Functional Features" in volume 13 on page 56.

▸ See the article "Urine Microbe-Derived Extracellular Vesicles in Children With Asthma" in volume 13 on page 75.

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Special attention has been focused on in the role of microbiome in human health and disease over the past decade, with significant advances in culture-independent technologies for investigating microbial communities mainly through analyzing the gut microbiota. The dysbiosis of the gut microbiota is associated with several diseases ranging from localized gastrointestinal to neurological, hepatic, and respiratory disorders.[1] Changes in the production of short-chain fatty acids and other metabolites due to an imbalance in the composition of these intestinal microbes have been suggested to be a possible pathogenic mechanism[2]; however, they can not explain diverse functions of microbes in the host.

Surprisingly, a recent article suggested that blood microbial profiles, not stool, could be harnessed to differentiate between diverse cancers, even after extensive internal validation check and decontamination. However, the authors could not determine whether the nucleic acids observed come from live microorganisms, host cells, or lysed bacteria in the blood.[3] Recent research suggests that the microbial DNA found in the article's plasma could come from extracellular vesicles (EVs) released from microbes rather than microbes themselves. Microbial EVs, nanometer-sized lipid bi-layered vehicles, can be absorbed, circulated and excreted through urine. These EVs deliver cellular components to cells throughout the body and contribute to intercellular communication with relevant effects on diverse diseases. Apart from the gut microbial composition changes in microbial EV composition have been suggested to be involved in the pathophysiology of human diseases such as cancer and type 2 diabetes.[4,5]

The role of microbial EVs as a mediator linking the gut to the lungs in allergic inflammation has also been suggested.[6] As blood microbial EVs have also been found in patients with allergic diseases,[7] it would be extremely interesting whether urine microbial EVs are present and could be harnessed in allergic diseases. Blood microbial EVs are usually detectable in humans; however, studies about urine microbial EVs are still lacking.[8] Only one recent study identified dysbiosis in the asthma group using microbe-derived EVs in children.[9]

Two papers published in this issue of the *Allergy, Asthma & Immunology Research* have shown the significance of urine microbial EVs in allergic diseases, which for the first time are the

studies show the presence of urine microbial EVs in allergic airway disease. Samra *et al.*[10] have demonstrated that urine microbial EVs have compositional and functional features in allergic airway disease associated with increased total immunoglobulin E level and peripheral eosinophil count (%). Similarly, Lee *et al.*[11] have revealed that altered urine microbial EVs are consistent with changes in the gut microbiota in children with asthma. In addition, lower microbial richness was noted in the urine of the asthma group compared to the healthy group. These findings are collectively important because urine microbial EVs could be applicable for differentiating patients with allergic disease from healthy controls based on differences in microbial diversity, specific microbiota patterns and functional profiles. These studies propose that measurement of urine EVs may be a quick and useful method to diagnose or predict allergic disease, as urine is an attractive sample for easily accessible collection. Unfortunately, both studies were limited due to their small sample size. Whether urine microbial EVs originate from the gut microbiota should also be further clarified.

Until now, the significance of EVs based on basic, clinical and translational data has accelerated processes for EV isolation and characterization. However, some limitations remain unsolved in EV research that is important to understand their relevance to human immunologic diseases. First, large-scale, prospective studies are mandatory. Secondly, a protocol to separate microbial EVs from various biological components in urine samples has not yet been standardized, although a size- and density-based method was suggested to remove body fluid complexity. Thirdly, clinical features, such as age and sex, which may influence microbial EV formation regardless of disease status, have not been identified due to limited numbers of study subjects in patients' cohorts. Clarification of associations between clinical features and EV characteristics is essential for understanding the function of microbial EVs in the pathogenesis of various allergic diseases. Finally, new approach should be designed to prove the reproducibility and quality of the EV study.

In conclusion, emerging evidence has demonstrated that microbial EVs are implicated in the trafficking of molecules between microbes and host, contributing to the pathophysiology of major allergic diseases. Physicians' enthusiasm for clinical application of these EVs as a diagnostic biomarker has not faded despite practical difficulties in isolating low-concentration microbial EVs. In particular, urine microbial EVs have a potential benefit for developing biomarkers because urine samples have many advantages in terms of simple collection, less contamination and being more acceptable to hard-to-reach populations. In the near future, improvements in EV isolation/characterization and applications of artificial intelligence technology are expected to offer a diagnostic or prognostic value beyond current measures.

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