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Review

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Bacterial Extracellular Vesicles: A Candidate Molecule for the Diagnosis and Treatment of Allergic Diseases

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ABSTRACT

Extracellular vesicles (EVs) are an end product released from almost all living cells such as eukaryotic cells and bacteria. These membrane vesicles containing proteins, lipids, and nucleic acids are mainly involved in intracellular communications through the transfer of their components from donor to acceptor cells. Moreover, EVs have been implicated in many functions in response to environmental changes, contributing to health and disease; bacterial EVs depending on their specific parental bacterium have diverse effects on immune responses to play a beneficial or pathogenic role in patients with various allergic and immunologic diseases. As bacterial EVs are a completely new area of investigation in this field, we highlight our current understanding of bacterial EVs and discuss their diagnostic and therapeutic potentials (as immunomodulators) for targeting asthma and atopic dermatitis.

Keywords: Asthma; atopic dermatitis; microbiome; diagnosis; extracellular vesicles; therapy

INTRODUCTION

Over the past decade, the subject of extracellular vesicles (EVs) has emerged as an exciting research area. Bacterial EVs were first identified in the 1960s, but their roles in nature have gained attention recently.[1] These membrane vesicles are nanoparticles delimited by a lipid bilayer and loaded with various molecules originating from bacteria.[2] Although the formation of vesicles seems to be a conserved process in both symbiotic and pathogenic bacteria, each bacterial EV has different characteristics, including structure, size, density, and molecular composition, according to the bacterial species inhabiting the host.[3] In the process, bacteria rapidly adapt to the environment to survive and grow, produce EVs, and even overproduce EVs under certain circumstances contributing to human health.[4] Moreover, accumulating evidence has shown that EV-mediated interactions between host and bacteria are associated with the pathogenesis of various diseases by regulating immune responses.[5-7] To date, bacterial EVs have also been shown to be relevant to allergic diseases, such as asthma and atopic dermatitis (AD), which impose a huge burden on society.[8,9] As allergic diseases have the possibility of causing morbidity and mortality worldwide, this review emphasizes immunological aspects of bacterial EVs in the development of diagnostics and therapeutics.

Disclosure

There are no financial or other issues that might lead to conflict of interest.

BACTERIAL EVs AND CHARACTERISTICS

For the clinical application of bacterial EVs, a better understanding of EV properties needs to be preceded. Indeed, studies on EV specificity may further provide the strategy for using bacterial EVs in many ways. However, the biology of bacterial EVs still needs to be determined as the systemic presence of bacterial EVs implies how little we know about these novel molecules that play a role in the interactions between bacteria and host. To date, most bacteria hosted by the human body are located on all surfaces in contact with the environment including the gastrointestinal tract, respiratory tract, and skin. Although commensal bacteria live quietly in the body when a person is healthy, subtle or dramatic pathophysiological changes could allow changes in EV production. Typically, these EVs derived from all bacteria have been known to be spherical with a nanometer-sized bilayer membrane.[10] Moreover, bacterial EVs were verified to contain multiple components, such as proteins, peptidoglycan, polysaccharides (lipopolysaccharides or lipoteichoic acids), phospholipids, nucleic acids (DNAs or RNAs), and metabolites, on the basis of structural and molecular studies. In gram-negative bacteria, EVs are naturally released from the outer membrane because of the presence of a thin outer cell wall.[11] However, the process of EV biogenesis is more complicated in gram-positive bacteria due to the presence of a thick peptidoglycan barrier. To explain how EVs traverse such a thick cell wall, the action of surfactant proteins and certain peptidoglycan-degrading enzymes, including endolysin and autolysins, has been proposed.[12] Therefore, excessive EV formation is thought to be due to abnormalities of the cell envelope in response to specific stresses. More work is required to understand the complex characteristics of bacterial EVs.

BACTERIAL EVs AND ALLERGIC DISEASES

Allergic diseases, including respiratory, skin, and food allergies, have progressively increased in prevalence over the last few years. Typically, chronic inflammation induced by persistent or repetitive exposure to specific allergens is shown to be associated with the development of allergic diseases.[13] However, the pathophysiology of allergic reactions is much more complicated as many factors, such as genetic, epigenetic, and environmental conditions, are responsible for inflammatory status. In an effort to explain the complex mechanism of allergic diseases, many recent studies have focused on the central role of the microbiome in the modulation of immune systems.[14] In particular, qualitative and quantitative changes in bacterial EV composition and function have been implicated in the development of allergic diseases (**Fig. 1**).

Asthma

Asthma is a chronic respiratory disease related to variable expiratory airflow impairment with bronchoconstriction and mucus production. To date, asthma has been known to present multiple phenotypes or endotypes with diverse clinical characteristics driven by individual susceptibility, environmental exposure, and bacterial dysbiosis.[15,16] In infants, subtle transient changes in specific bacteria are associated with the development of the disease in the first few months of life. Especially, the relative abundance of the genera *Lachnospira*, *Faecalibacterium*, *Rothia,* and *Veillonella* was potentially linked to the risk of asthma.[17] In adults, the overall composition of the microbiota between asthmatic patients and healthy subjects shares many parts; however, the relative proportion of *Bifidobacterium* is associated with asthma susceptibility.[18,19] In addition to changes in the bacterial communities, recent

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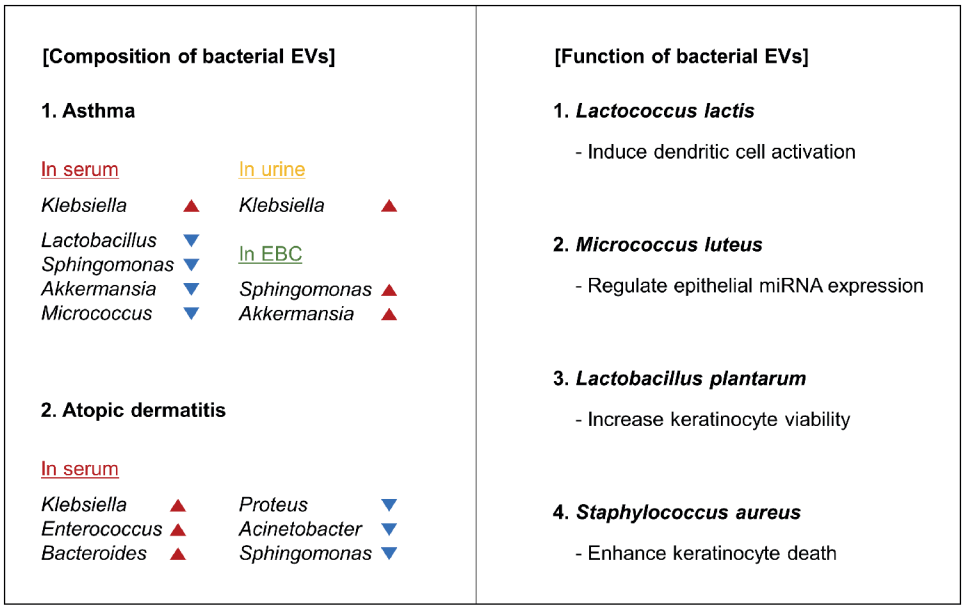

Fig. 1. Composition and function of bacterial EVs in patients with allergic diseases.
EV, extracellular vesicle; EBC, exhaled breath condensate.

studies revealed the distinct composition of bacterial EVs in asthmatic patients. In serum, increased levels of EVs derived from *Klebsiella* as well as lower levels of EVs derived from *Lactobacillus*, *Sphingomonas*, *Akkermansia,* and *Micrococcus* were found in asthmatic patients.[20] Similarly, increased EVs derived from *Klebsiella* were detected in urine samples from asthmatic patients.[21] However, EVs derived from *Sphingomonas* and *Akkermansia* were significantly higher in exhaled breath condensate from asthmatic patients.[22] These EVs are important for the pathogenesis of lung diseases because significant changes in the proportion of bacterial EVs have also been noted in patients with chronic obstructive pulmonary disease (COPD) and lung cancer.[23,24]

So far, several mechanisms have been proposed to explain how each microbiome contributes to the development of asthma. Commensal bacteria secrete various metabolites, including short-chain fatty acids, which affect immune responses by regulating the activation status of dendritic and Treg cells.[25-27] Moreover, vitamins and amino acids generated by commensal bacteria are possibly involved in the development and homeostasis of immune cells.[28] Although it remains controversial which components in bacterial EVs play a specific role in individual allergic disease, their immunomodulating effects have been noted in asthmatic patients. It is well known that for type 2-high/eosinophilic responses along with type 2 cytokines (interleukin [IL]-4, IL-5, and IL-13), mast cells and epithelial cells play a significant role in asthmatic airways.[29-32] EVs derived from *Lactococcus lactis* have been demonstrated to modulate a T helper (Th)1/Th2 balance by stimulating dendritic cells.[33] In contrast, type 2-low/neutrophilic asthma is characterized by the type 1 or type 17 response with steroid resistance; however, understanding mechanisms underlying neutrophilic airway inflammation is still lacking, and there is no targeted treatment available.[34-37] A recent paper has suggested that EVs derived from *Micrococcus luteus* could regulate epithelial cell activation to express microRNAs which are important for controlling airway inflammation in neutrophilic asthma.[38] There have been various study results showing the presence of bacterial EVs in chronic lung diseases such as asthma, but these findings are not consistent

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across studies. However, we suggest bacterial EVs could impact chronic airway diseases, such as asthma and rhinitis, by regulating immune responses at target tissues.

AD

AD is a chronic inflammatory skin disease characterized by recurrent eczematous lesions and pruritus symptoms. Moreover, accumulating data have shown that AD patients have disturbed bacterial compositions and diversities in the skin and the guts, resulting in disease onset and progression to atopic march. Especially, AD patients have been reported to have large amounts of *Staphylococcus aureus* on the skin.[39] Although the skin microbiota, which lives on the tissue surface and interacts with external environments, could be the direct evidence for the development of AD, changes in the composition of the gut microbiota have also been reported in AD patients. In particular, the relative abundance of the genus *Bifidobacterium* was significantly lower in AD patients than in healthy subjects.[40] In addition, another previous study has suggested *Faecalibacterium prausnitzii* as the major gut species strongly involved in the chronic progression of AD through impairing the gut epithelial barrier.[41] Currently, the composition of circulating bacterial EVs is being further analyzed in AD patients.[42] In this study, the prevalence of EVs derived from *Klebsiella*, *Enterococcus,* and *Bacteroides* was higher, whereas EVs derived from *Proteus*, *Acinetobacter,* and *Sphingomonas* were lower in AD patients. To date, the role of *S. aureus* in the pathogenesis of AD has been highlighted as this bacterium dominantly contributes to skin barrier damage and inflammation by producing a number of virulence factors.[43] Among them, α-hemolysin in the EVs derived from *S. aureus* has been demonstrated to induce keratinocyte death as well as type 2 and 1/17 responses.[44,45] However, EVs derived from *Lactobacillus plantarum* could restore cell viability *in vitro* and inhibit IL-4 production in *S. aureus*-mediated skin inflammation *in vivo*.[46] In this aspect, further investigations into local and systemic fluctuations of bacterial EVs with their novel functions may provide insight into the mechanism or therapeutic potential for AD.

BACTERIAL EVs AND CLINICAL IMPLICATIONS

Recent technological advances in next-generation sequencing have strengthened our ability to detect the microbiome in a variety of biofluids. As metagenomic analyses have been more developed, microbiome diagnostics is expected to be a promising field for finding new biomarkers.[47] Moreover, the microbiome has been considered a therapeutic target for managing allergic diseases, and certain species have been proposed to modulate immune responses. Various approaches have already been attempted to restore the microbiome in the gut using probiotics, prebiotics, and synbiotics.[48] However, clinical applications of bacteria themselves have some limitations because a number of bacteria do not simply represent their activity and efficacy. In addition, it is unclear whether bacteria can survive in the human body after local or systemic administration.[49] Due to such issues, a recent paper has suggested bacterial EVs as a new tool in medicine, providing us with innovative diagnostic and therapeutic solutions in precision medicine.[50] Here, we further propose bacterial EVs as a substitute for bacteria with the advantage of presenting active biological information.

Diagnosis

Based on the metagenomic approach to analyzing 16S ribosomal RNA genes, certain bacteria, and their EVs have been recognized as important players in the pathogenesis of various human diseases.[51] Although the tools and databases are becoming more elaborate and complicated in providing information on the compositional and functional aspects of

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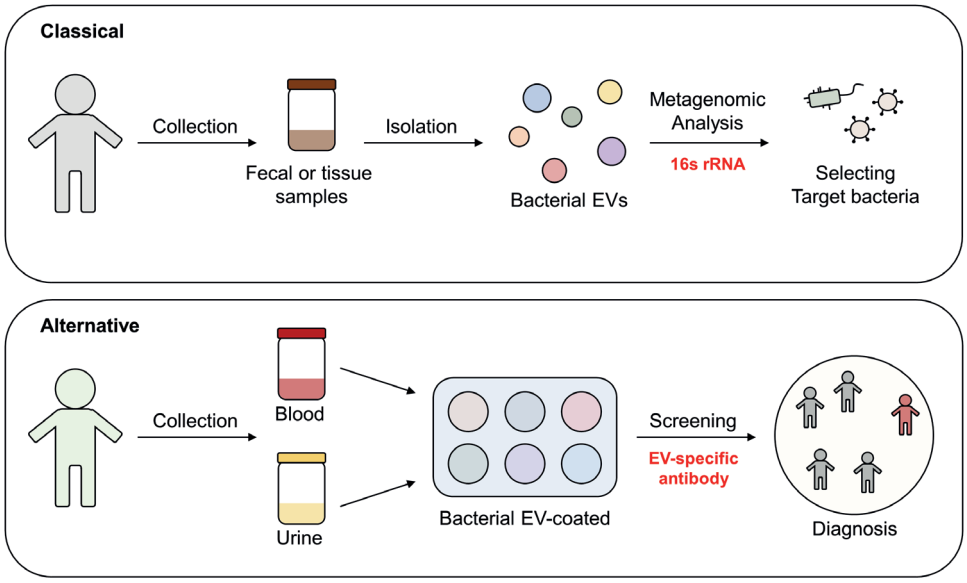

Fig. 2. Bacterial EVs for the diagnosis of allergic diseases. Metagenomics has been extensively performed to find target bacteria associated with human diseases. However, the detection of bacterial EV-specific antibodies in biofluids of patients has recently been proposed to investigate target bacteria.
EV, extracellular vesicle; rRNA, ribosomal RNA.

bacterial communities, these methods still remain time and cost issues, which are major hurdles in association with sequencing technology.[52] Considering such issues, recent studies have attempted to analyze bacterial EVs instead of measuring the relative abundance of RNA genes (**Fig. 2**). For example, evaluating the concentration of bacterial EV-specific immunoglobulin (Ig)G antibodies in serum has provided a novel diagnostic approach to allergic diseases. In AD patients, markedly elevated levels of IgE against EVs derived from *S. aureus* have already been demonstrated.[44] A previous study reported total IgG levels against dust-derived EVs in patients with asthma, COPD, and lung cancer compared to healthy subjects.[53] As a result, the levels of serum IgG against dust-derived EVs were significantly higher in all the study groups than in healthy subjects, suggesting that IgG sensitization to dust EVs is an independent risk factor for developing asthma and COPD. When bacterial EV-specific IgG/IgG subclass antibodies in serum were evaluated,[24] significantly higher levels of total IgG to EVs derived from *S. aureus*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* were noted in asthmatic patients compared to healthy subjects, which needs further replication studies. In addition, a recent study has shown significantly lower levels of IgG4 (but not IgG1) against EVs derived from *L. lactis* in asthmatic patients than in healthy controls.[33] In comparison, levels of IgG4 against *M. luteus*-derived EVs were significantly lower in patients with neutrophilic asthma than in those with eosinophilic asthma.[38] Considering that these antibodies could represent long-term exposure to external factors, we suggest bacterial EV-specific IgG4 levels as a potential serum biomarker for identifying asthmatic patients.[54]

Therapy

A comprehensive understanding of immunological mechanisms underlying allergic diseases has allowed a strategy for targeting specific molecules in these processes.[55-59] To date, multiple therapeutic agents, including biologics that regulate immune cell and epithelial cell activation, have been proposed to manage patients with allergic diseases[60-63]; however, some patients are refractory to conventional pharmacologic or immunomodulating treatment. In this aspect, unmet medical needs for the development of new therapeutic

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targets differentiated from conventional ones are being raised. We expect bacterial EVs to serve as next-generation therapeutics for diseases with unmet medical needs. Although the possibility of using mammalian EVs in therapeutic applications has been extensively proposed, bacterial EVs have not yet received much attention.[64] Nevertheless, some recent papers have shown the beneficial effects of bacterial EVs on regulating immune responses in allergic diseases. In allergic asthma, EVs derived from *L. lactis* have been revealed to shift from Th2 to Th1 responses by activating dendritic cells to produce IL-12, which is critical for directing the development of Th1 cells.[33] In neutrophilic asthma, EVs derived from *M. luteus* have been demonstrated to inhibit monocytes from releasing IL-1β, followed by suppression of group 3 innate lymphoid cell activation.[38] Moreover, these EVs could modulate microRNA expression in airway epithelial cells, and certain microRNAs have the function in inflammatory conditions to reduce monocyte activation. In AD, EVs derived from *L. plantarum* have been suggested to decrease skin inflammation as well as epidermal thickness despite the lack of evidence.[46] In food allergy, EVs derived from *Bifidobacterium longum* have been shown to alleviate the occurrence of diarrhea by inducing mast cell apoptosis without affecting T cell-mediated immune responses.[65] Although this review summarized clinical applications of beneficial bacteria-derived EVs as potential immunomodulators, suppressing harmful bacteria-derived EVs through inhibiting their production or function could be another therapeutic strategy.[66] Furthermore, bacterial EVs could be applied as vehicles to deliver genetic materials of vaccine components into target cells.[67,68] Here, we summarized the strategies for using bacterial EVs in allergic diseases (**Fig. 3**).

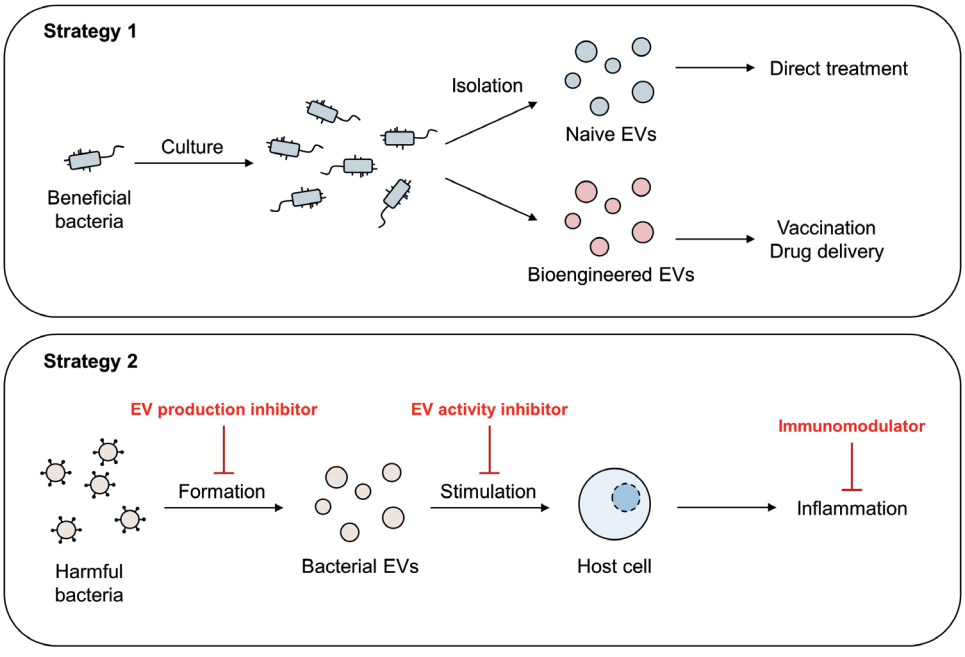

Fig. 3. Bacterial EVs as immunomodulators for allergic diseases. In strategy 1, EVs derived from beneficial bacteria, including probiotics, could be used for treatment. In strategy 2, inhibition of bacterial EV production and activity as well as a reduction in EVs-mediated inflammation has been suggested.
EV, extracellular vesicle.

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CONCLUSION

Bacterial EVs, a novel agent enhancing intracellular communications between host and bacteria, play a critical role in immune responses and intracellular processes responsible for major allergic diseases. They are stable in biofluids (without degradation), representing an individual's current inflammatory status; therefore, it is suggested that they may have the potential for diagnostics and therapeutics. Further investigations are needed to solve several questions raised: 1) are bacterial EVs sensitive to given isolating and manufacturing processes; 2) how specific cargos (proteins and/or genetic materials) are selectively packaged into the EVs; and 3) why different biological effects on distinct recipient cells are produced by EVs containing identical contents. The answers will help us understand the exact function of EVs according to each allergic disease in clinical practice.

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