Editorial
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Extracellular Vesicle: An Unknown Environmental Factor for Causing Airway Disease

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Most cells from different organisms release extracellular vesicles (EVs) to the extracellular environment. The term EV is a broad one for all types of vesicles found in body fluids and cell culture in accordance with the recommendation of the International Society for Extracellular Vesicles (ISEV).[1] In recent years, Interest in EVs increased because of their function in intercellular communication and their potential use as biomarkers and therapeutics for several diseases.[2,3]

These EVs contain various DNAs, proteins, mRNAs, and microRNAs (miRNAs) that have potential diagnostic and therapeutic implications and are classified into exosomes, microvesicles, and apoptotic bodies through their biogenesis and secretion mechanisms. Exosomes are 50 to 150- nm vesicles released by living cells. Microvesicles are 100-to 2,000-nm vesicles formed by direct outward budding of the plasma membrane from living cells. Apoptotic bodies are 1-to 4-μm vesicles and released from the plasma membrane as apoptotic cell blebs.[4]

EVs act as a signaling complex, transfer membrane receptors between cells, deliver proteins to target cells, and modify the receiving cells by horizontal transfer of genetics.[5]

Many studies have suggested that EVs might be involved in a wide range of biological processes, including immune regulation, inflammation, and tumor development.[6] EV have been isolated from different body fluids, such as plasma,[7] urine,[8] and bronchoalveolar lavage fluid (BALF).[9] EVs are highly stable in biological fluids and protected from degradation by their lipid bilayer.[4] They play important roles in maintaining homeostasis through intercellular communication in the human airway.

Recently, their biological roles draw significant interest in respiratory diseases because their contents, including miRNA, play an important role in the pathogenesis of many respiratory diseases, including lung cancer, interstitial lung disease, chronic obstructive pulmonary disease, and allergic diseases like asthma.[10] In the lungs, various types of cells, such as epithelial cells, fibroblasts, endothelial cells, tumor cells, stem cells, and immune cells, can release EVs. Alveolar macrophage-derived EVs can potentially control lung and airway inflammation through intercellular communication. Exposure to various stimuli, such as infection, DNA damage, and smoke exposure, enhances EV secretion and modify EV composition to change the surrounding microenvironment through EV-mediated cell-to-cell communication.[11-13]

Noncancerous cell-derived EVs in the airway show protective functions against injuries, such as tissue recovery and repair, but lung cancer- derived EVs regulate tumor malignancy.[14] Exosome secretion is increased during allergic inflammation in the lungs, which may mediate increased intercellular signaling.[6] A few studies have reported that EVs may regulate airway inflammation and allergic reactions through their paracrine effects in the lungs.[15,16] BALF exosomes from healthy individuals and asthmatic patients exhibit distinct phenotypes and functions. In asthmatics, BALF exosomes may contribute to subclinical inflammation in airway epithelium.[17]

In 2010, Pegtel *et al.*[17] reported that miRNAs of viral origin are found in EVs secreted by infected cells and that their transfer to non-infected cells led to the regulation of some target genes of these miRNA. It has recently been shown that, EVs derived from *Escherichia coli* into the bloodstream induced systemic inflammation mimicking sepsis[18] and that *Staphylococcus aureus*-derived EVs are related to the pathogenesis of atopic dermatitis-like inflammation.[18,19]

In 2013, Kim *et al.*[20] reported the relationship between EVs in indoor dust and neutrophilic pulmonary inflammation. Their study indicated that inhalation of indoor-dust EVs induce both Th1-and Th17-cellresponses and neutrophilic inflammation in the lungs. Furthermore, clinical data suggest that IgG1 sensiti-

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zation to dust EVs may be related to the clinical manifestation of asthma symptoms in atopic children. Indoor-dust EVs may represent a novel target for the development of diagnostic tool for neutrophilic inflammation-induced airway diseases, such as neutrophilic asthma and COPD.

In this current issue of the *Allergy, Asthma & Immunology Research*, Kim *et al.*[21] reported that serum IgG antibody level to dust EVs in the 3 disease groups and healthy controls had a normal distribution and were significantly higher in patients with non-eosinophilic asthma, COPD or lung cancer than in healthy control subjects. Furthermore, multivariable analysis showed that a high serum anti-dust EV IgG concentration was an independent risk factor for non-eosinophilic asthma, COPD (irrespective of severity), and lung cancer (irrespective of cellular subtypes) after adjustment for age, gender, and cigarette smoking. Although additional prospective studies will be needed to determine whether dust EV exposure has a causal relationship with asthma, COPD, and lung cancer, these findings provide an new insight into the pathogenesis of non-eosinophilic asthma, COPD, and lung cancer, as well as a clue to developing novel diagnostic and/or therapeutic modalities.

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