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Exosomes: an important messenger in the asthma inflammatory microenvironment

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Abstract

Asthma is a frequently diagnosed chronic pulmonary disease that is increasing in incidence. It is characterized by airway narrowing due to an immune response to allergens, infections, or air pollutants. Several types of cells participate in the initiation and development of asthma, including bronchial epithelial cells, smooth muscle cells, and immune cells (mast cells, T and B cells, and dendritic cells). Exosomes released in the asthmatic microenvironment exert a crucial function in intercellular signaling by transporting their contents, such as RNA, DNA, proteins, and lipid mediators, to recipient cells, which play key roles in the pathogenesis of asthma. In the present review, we summarize currently available information on the function of exosomes in the asthmatic microenvironment.

Keywords

Exosome, asthma, inflammatory environment, allergen, airway, immune cells

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Introduction

Asthma is one of the most frequently diagnosed pulmonary disorders, with a high incidence (~40%) in children from Western countries. Allergic reactions are caused by

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different stimuli, such as allergens, pollen, irritants, pathogens, and air pollutants, and many patients with asthma suffer from allergic manifestations, such as rhinitis and food allergies.[1,2] As a complex and multifactorial disease, asthma is triggered by various elements. A highly diverse immune cell repertoire and structural cells are involved in orchestrating inflammatory responses in asthma. Not only the cellular component but also the soluble inflammatory microenvironment is important in the pathogenesis of asthma.[3–5] Exosomes, which are nanoscaled vesicles (30–100 nm in diameter) produced by various cells, contain enriched amounts of biomolecules, including abundant sphingomyelin, phosphatidylserine, cholesterol, and ceramides on the lipid bilayer surface of exosomes. Exosomes contain adhesion molecules, integrins, tetraspanins (e.g., CD9, CD63, CD81), and major histocompatibility complex (MHC) antigens of class I and class II in the membrane. Exosomes also contain a few types of proteins, such as heat-shock proteins (HSP70 and HSP90) and cytoskeletal proteins (actin, gelsolin, myosin, and tubulin) and may contain some enzymes, such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH), nitric oxide synthase, and catalase. Moreover, exosomes contain DNAs, mRNAs, micro(mi)RNAs, long noncoding (lnc)RNAs, and circular (circ)RNAs (Figure 1).[6] Exosomes are recognized as crucial regulators in intercellular communication, and they can load their cargoes into recipient cells both proximally and distally.[7] Exosomes exert their functions depending on the cell state and their parental cell type, and they can induce immune activation or suppression or tolerance-inducing effects. The layer of bronchi and alveoli facing the lumen is composed of epithelial cells, which are at the interface between the environment and lung tissue. Epithelial cells can modulate the inflammatory response to exterior stimulants, such as allergens or cigarette smoking,

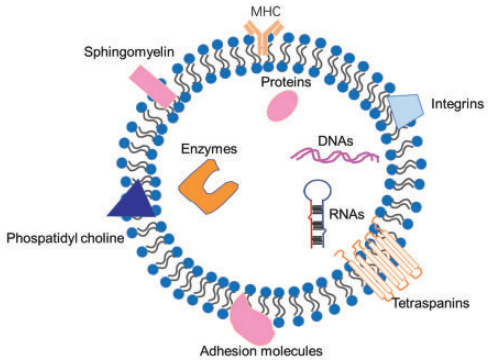

Figure 1. Illustration of an exosome. Exosomes are small vesicles with a double-layer phospholipid membrane structure, which is enriched in sphingomyelin, phosphatidylserine, cholesterol, and ceramides. Exosomes contain enriched amounts of biomolecules, including proteins and nucleic acids. They contain adhesion molecules, integrins, tetraspanins (e.g., CD9, CD63, CD81), and MHC antigens class I and class II (MHCI and MHCII). There are several types of proteins, such as heat-shock proteins (HSP70, HSP90), cytoskeleton proteins (actin, gelsolin, myosin, tubulin), and some enzymes, such as glyceraldehyde 3-phosphate dehydrogenase, nitric oxide synthase, and catalase. Exosomes also contain DNAs, mRNAs, microRNAs, long noncoding RNAs, and circular RNAs. These cargos in exosomes can be transported into target cells. MHC, major histocompatibility complex.

actively contributing to the pathogenesis of these diseases. Moreover, accumulating data have shown that lung epithelial cells can actively regulate the local immune response[8] and may transfer important signals from the environment to cells in deeper tissue through exosomal signaling.

As a pulmonary inflammatory disease, allergic asthma is characterized by bronchoconstriction-triggered respiratory obstruction, inflammation-induced edema formation, and mucus hypersecretion, as well as the presence of allergen-specific serum IgE. In the lung, several types of cells participate in asthmatic progression, such as epithelial cells, dendritic cells

(DC), CD4+ and CD8+ T lymphocytes, macrophages, natural killer cells, and myeloid-derived regulatory cells (Figure 2).[3–5] Previous studies have revealed that a number of proteins involved in asthma and allergic inflammation are associated with exosomes, such as heat-shock protein 70 (Hsp-70)[9] transforming growth factor (TGF)-β,[10] and enzymes in leukotriene (LT) biosynthesis.[11] Nevertheless, it is largely unknown how exosomes regulate cell–cell communication in respiratory diseases. In this article, we review exosome-triggered cellular signaling between structural cells and immune cells in the pathogenesis of asthma.

Epithelial cell-derived exosomes in allergic respiratory inflammation

Airway remodeling driven by inflammatory cells and cytokines is often described in inflammatory respiratory disorders, including asthma and chronic obstructive pulmonary disease. The respiratory epithelium is the major barrier to external stimuli and toxins. These cells can regulate the inflammatory response to exterior stimulants, actively contributing to the progression of asthma and allergic respiratory inflammation.[12]

Exosomes are mainly derived from bronchial epithelial cells (BECs) in the lungs of

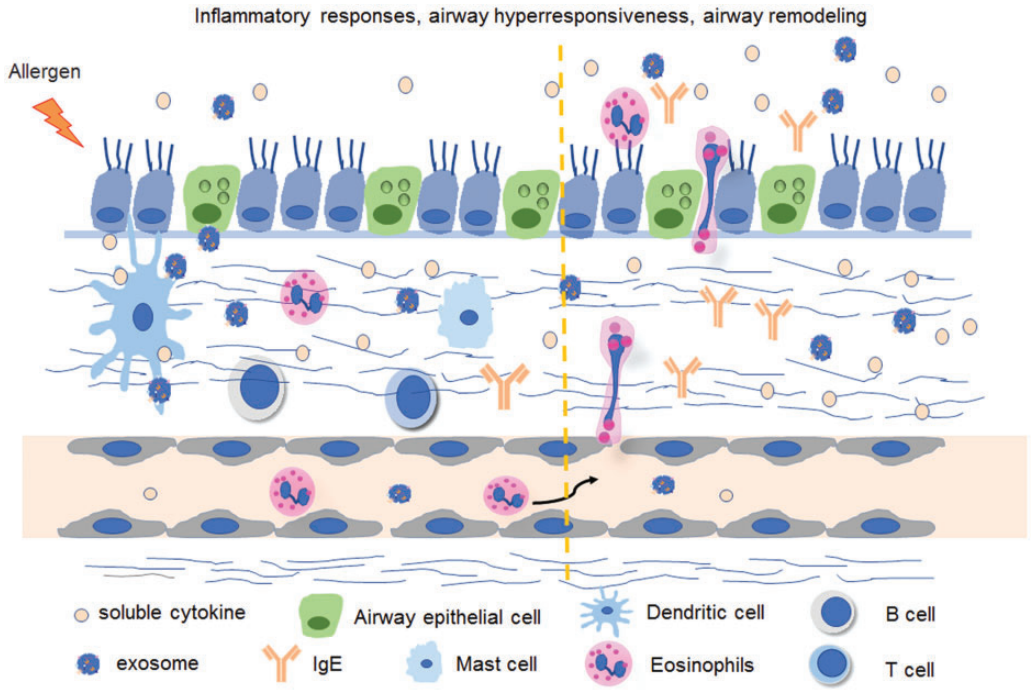

Figure 2. The pathological process of asthma. The allergen stimulates the recruitment of inflammatory cells such as eosinophils, the proliferation and activation of immune cells such as mast cells and DCs, and induces the injury of airway epithelial cells, which leads to the release of inflammatory factors and exosomes. The exosomes can induce the proliferation and chemotaxis of mast cells, which further stimulate B cells to produce IgE. Exosomes derived from DCs induce the production of Th2 cytokines. These changes result in the inflammatory response, airway hyperresponsiveness, and remodeling. DCs, dendritic cells; Th, T helper.

patients with asthma. The proliferation and chemotaxis of monocytes can be induced by exosomes released from BECs without impairing monocyte differentiation. In addition, the sphingomyelinase inhibitor GW4869 can suppress exosome secretion by suppressing sphingomyelinase, alleviating asthmatic conditions and resulting in impaired proliferation of monocytes.[12] Further study has shown that epithelial cells challenged by interleukin (IL)-13 can secrete exosomes, leading to stimulated proliferation of inflammatory cells, and GW4869 can dampen such inflammation.[12]

Another study indicated that expression of TGF-β2 at the transcriptional and translational levels in fibroblasts was similar between healthy individuals and patients with severe asthma. However, the expression of TGF-β2 was decreased in exosomes derived from fibroblasts of severely asthmatic patients compared with controls. Exosomes secreted by fibroblasts from patients with severe asthma significantly enhanced the proliferation of epithelial cells from both healthy and severely asthmatic patients compared with controls. In addition, the proliferation of epithelial cells was suppressed by enhanced TGF-β2 expression in exosomes though overexpression of TGF-β2 in fibroblasts of patients with severe asthma, whereas depletion of TGF-β2 increased the proliferation of epithelial cells.[13]

Bronchoalveolar lavage fluid-derived exosomes in allergic respiratory inflammation

A few investigations have assessed the impacts of secreted exosomes on allergic airway inflammation in bronchial asthma.[12,14,15] Kulshreshtha et al.[12] sensitized mice intraperitoneally with ovalbumin (OVA) and aluminum hydroxide after OVA challenge and analyzed exosomes in bronchoalveolar lavage fluid (BALF). Exosome secretion into BALF was elevated upon OVA challenge. Moreover, this study showed that secretion of exosomes into BALF was reduced and respiratory inflammation improved by administration of GW4869. These data suggest that intracellular signaling via exosomes integrally participates in the pathogenesis of allergic respiratory inflammation. Similar findings were found in another asthmatic mouse model. Exosomes were isolated from BALF of control and house dust mite (HDM) allergen-exposed HDM-sensitized mice. Compared with the sham-control mice, the number of exosomes was elevated 8.9-fold in BALF from HDM-challenged mice. Moreover, the number of exosomes in BALF after HDM exposure was decreased by GW4869 treatment.[16]

As small noncoding RNAs, microRNAs (miRNAs) modulate gene expression through two approaches: suppression of translation and degradation of mRNA. A single miRNA can modulate many genes, and multiple miRNAs can modulate the same gene through additive or synergistic effects.[17] MiRNAs have been used as therapeutic targets and diagnostic markers for a wide range of diseases, including pulmonary disorders. A recent study using rodent models of asthma and inflammation showed that miRNAs play important roles in specific pathogenic events.[18]

A microarray study showed that expression of 139 miRNAs in BALF-derived exosomes and 175 miRNAs in lung tissues of HDM-sensitized mice was significantly changed. Interestingly, 54 miRNAs were common to both samples, and their expression was increased in exosomes and decreased in lung tissues upon HDM exposure. Further study demonstrated that HDM stimulation decreased the expression of miR-346, miR-1827, and miR-574-5p in exosomes of BALF, which could suppress molecules involved in T helper (Th)2

inflammation, such as IL-5 receptor and IL-13, and when released to the airway, these Th2 cytokines may be involved in the development of allergic respiratory inflammation in HDM-challenged mice.[16]

A recent study has shown that expression of exosomal miRNAs is altered in BALF of patients with asthma. The authors determined exosomal miRNA expression in healthy controls and patients with mild intermittent asthma at baseline and after environmental challenge. They assessed the extracted exosomal RNA using microarrays of probes for 894 human miRNAs; real-time PCR was used to validate their findings. Significant variations were detected in 24 BALF exosomal miRNAs. Remarkably, 16 miRNAs (including family members of let-7 and miR-200) could be used to differentiate patients with asthma from healthy controls. Therefore, exosomal miRNAs could be used to distinguish healthy individuals and patients with asthma.[15] Moreover, let-7 family (a-e) and miR-200 family (200b and 141) are the most outstanding miRNAs by which to distinguish between asthmatic patients and healthy controls in multivariate models. Kumar et al.[19] recently showed that let-7 family members were downregulated in an ovalbumin-sensitized murine model of asthma, leading to exacerbated respiratory inflammation. In contrast, inhalation of a let-7 mimic improved respiratory inflammation and hyperresponsiveness, attenuated mucus metaplasia and subepithelial fibrosis, and decreased IL-13 level. Furthermore, the let-7 family of miRNAs is important in patients with allergic asthma; these miRNAs directly target IL-13–producing cell types and inhibit secretion of IL-13.[19] The miR-200 family has also been shown to be involved in airway remodeling by regulating the epithelial–mesenchymal transition in asthmatic patients.[20,21] The level of miR-21 is reduced in patients with asthma at baseline, and the regulatory role of IL-13 upon miR-21 expression has been demonstrated in mouse models.[22,23] Exosomal miR-34b-5p and miR-34c-5p have recently been shown to be modulated by IL-13 in primary airway epithelial cells (AECs).[24] Kesimer et al.[3] demonstrated that BALF-derived exosomal miRNAs differ between patients with asthma and healthy controls. Greene and Gaughan[18] indicated that BALF-derived exosomes from asthmatic patients differ from those of healthy controls in terms of phenotype and function. Higher expression of exosome-associated markers has been found in exosomes from patients with asthma. There is no major difference between BALF exosomes before and after allergen provocation. However, the phenotype and function of BALF exosomes from asthmatic patients are altered relative to that of healthy controls. In addition, BALF exosomes from asthmatic patients significantly enhance the release of LTs and IL-8 in BECs, whereas the cysteinyl LT receptor 1 antagonist montelukast reduces release of exosome-induced IL-8, suggesting that BALF exosomes are involved in inflammatory processes in the lung.[25]

Monocyte-derived exosomes in allergic respiratory inflammation

Monocyte-derived DCs (MDDCs) and monocyte-derived macrophages (MDMs) are frequently used in in vitro models of DCs and macrophages. Previous works have indicated that exosomes secreted by DCs and macrophages have immunological functions.[26] Exosomes from MDDCs and MDMs contain LT A4 hydrolase (LTA4H) and LT C4 synthase (LTC4S), the downstream enzymes for LT biosynthesis, which can metabolize LTA4 to the pro-inflammatory LTs B4 and C4. Studies further show that TGF-β1 and IL-4, together with granulocyte-macrophage colony-stimulating factor (GM-CSF), are

the fundamental cytokines determining the phenotype of antigen-presenting cells (APCs), and they govern the expression and activity of LT pathway enzymes in APCs and their exosomes.[11]

A previous study has shown that DC-derived exosomes can activate naïve T cells and facilitate the transfer of functional peptide–MHC complex between DCs.[27] Likewise, exosomes from macrophages infected with intracellular pathogens can release exosomes that trigger a pro-inflammatory response.[28]

Mast cell-derived exosomes in allergic respiratory inflammation

Mast cells are granulated cells that can release histamine and heparin. They are ubiquitously distributed in all vascularized tissues, bone marrow and lymphoid tissue near blood vessels, smooth muscle cells, mucous glands, and hair follicles.[29]

As key effector cells in Th2- and IgE-associated immune responses, mast cells are involved in the synthesis of pro-inflammatory regulators stored in secretory granules, such as histamine and heparin.[29] Antigen presentation by bone marrow-derived mast cells (BMMCs) is tightly regulated by inflammatory molecules. IL-4 and GM-CSF are predominant triggers of this antigen presentation, whereas interferon (IFN)-γ fully abolishes this function.[30]

Exosomes derived from mast cells interact with airway smooth muscle cells (ASMCs) and induce them to release pro-inflammatory cytokines, including IL-6 and IL-8, which can exacerbate respiratory inflammation and recruit inflammatory cells to perpetuate asthma symptoms.[31]

Tkaczyk et al. demonstrated that cell culture supernatant of mast cells can substitute the cell–cell contacts to activate B and T lymphocytes.[32] Exosomes are originally stored within the cytoplasmic granules of mast cells. Upon stimulation with IL-4 and mast cell lines, BMMCs can spontaneously and constitutively release membrane vesicles or exosomes that can trigger B and T lymphocyte proliferation and cytokine secretion. More recently, this mast cell-induced lymphocyte activation has been shown to occur in vitro as well as in vivo, and such activation can be achieved by cultured mast cells and by peritoneal resident mature mast cells.[32]

Activation of lymphocytes is regulated by mast cell-derived factor(s), and cell surface contact is not required between mast cells and lymphocytes. In addition, the generation of IL-2, IFN-γ, and IL-12 supports that mast cells and mast cell-derived exosomes preferentially trigger Th1-type responses.[33] The exosomes released by BMMCs were shown to be transferred through high-affinity IgE receptors (FcεRI) to the inflammatory microenvironment and bind to free IgE to decrease Th2 cytokines (IL-4, IL-5, and IL-13), reduce inflammatory infiltration of eosinophils, and increase Th1 cytokines (IL-10 and IFN-γ) in a mouse model of allergic asthma induced by OVA exposure.[34]

A recent study has shown that DCs secrete several exosomal proteins, including MHC class II, Mac-1, CD9, MHC class I, and CD86, which can trigger phenotypic and functional maturation of DCs.[35] Compared with those derived from other cell types, including B lymphocytes and macrophages, only exosomes derived from BMMCs and peritoneal mast cells can induce activation of B and T lymphocytes. Moreover, mast cell-derived exosomes have no immunostimulatory activity if they are not pre-challenged with IL-4, suggesting that such function is a cytokine-mediated process.

Mast cell-derived exosomes may be regarded as immunologically sophisticated vectors for various antigens, which can be used by these cells to monitor the environment with higher efficiency.

Eosinophil-derived exosomes in allergic respiratory inflammation

As the end-stage cells in the propagation of inflammatory responses in patients with asthma, eosinophils are crucial effector cells. Eosinophils can synthesize and store intracellular granules, including major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin, and eosinophil cationic protein (ECP), and immediately secrete a diverse repertoire of cytokines (IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-18, and TGF-α/β),

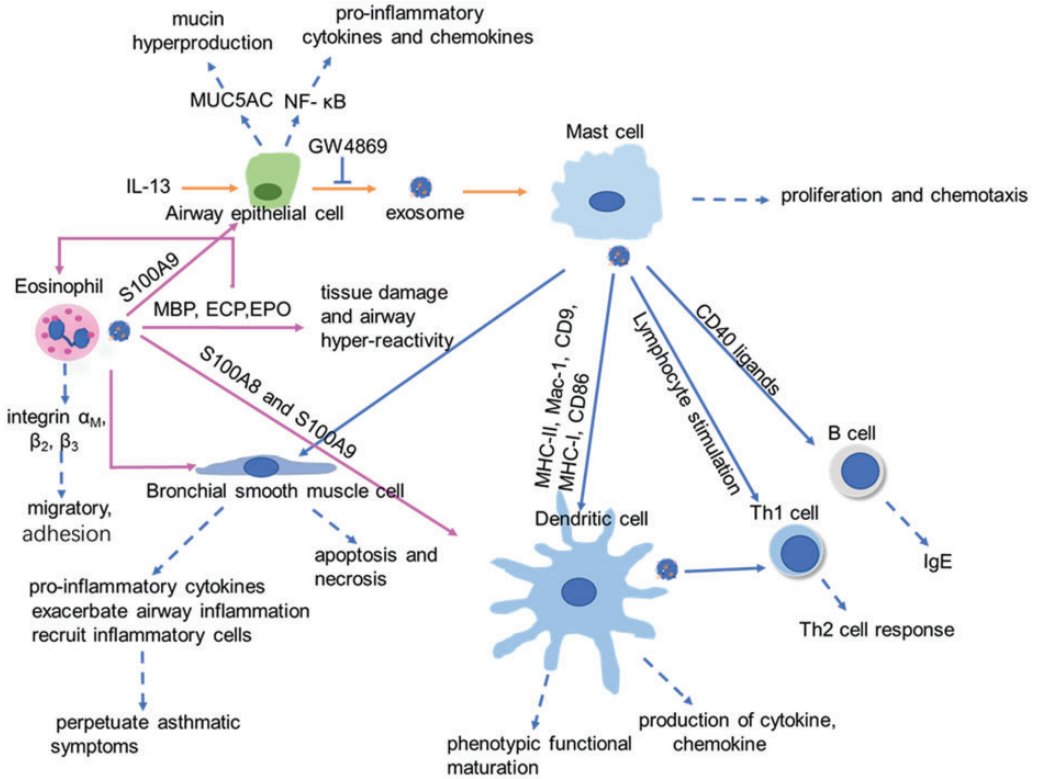

Figure 3. Interactions between structural cells and immune cells via exosomal communication during asthma. Exosomes derived from IL-13–treated AECs can induce proliferation and chemotaxis of mast cells. Exosomes released by mast cells can stimulate B cells to produce IgE through a T-cell-independent mechanism via CD40 ligands; induce T cell proliferation; increase production of IL-2, IL-12, and T cell responses; promote phenotypic functional maturation of DCs through MHC class II, Mac-1, CD9, MHC-I, and CD86; trigger the release of pro-inflammatory cytokines from smooth muscle cells; and exacerbate airway inflammation. Exosomes derived from DCs induce the production of Th2 cytokines. Exosomes derived from eosinophils induce tissue damage, airway hyperreactivity, and several integrins related to cell adhesion via MBP, ECP, and EPO; promote the release of pro-inflammatory cytokines, chemokines, and mucin hyperproduction from AECs; and trigger the production of cytokines and chemokines of DCs through S100A8 and S100A9. In addition, exosomes released by eosinophils induce the apoptosis and necrosis of bronchial smooth muscle cells. IL, interleukin; AECs, airway epithelial cells; DCs, dendritic cells; MHC, major histocompatibility complex; Th, T helper; MBP, major basic protein; ECP, eosinophil cationic protein; EPO, eosinophil peroxidase; NF-κB, nuclear factor kappa-B; MUC5AC, mucin 5AC; GW4869, inhibitor of neutral sphingomyelinase (nSMase).

chemokines (RANTES and eotaxin-1), and other important regulators (LTC4, platelet-activating factor, thromboxane B2, and prostaglandins).[36,37]

Mazzeo et al. indicated that eosinophils from patients with asthma secrete more exosomes than those from healthy controls.[14] Moreover, stimulation of eosinophils by IFN-γ in healthy subjects can also increase the release of exosomes, and no differences in the size distribution of exosomes have been observed between healthy individuals and asthmatic patients. Furthermore, the expression of EPO, MBP, and ECP in eosinophil-derived exosomes from healthy individuals and asthmatic patients is not different.[14] Eosinophil-derived exosomes of patients with asthma can increase the apoptosis and necrosis of bronchial smooth muscle cells (BSMCs) and delay the proliferation of small AECs.[38] Moreover, exosomes can cause tissue damage and airway hyperreactivity to aggravate asthma by carrying MBP, ECP, and EPO.[37] In addition, exosomes can induce secretion of reactive oxygen species from eosinophils, increase the migratory and adhesive capacities, and elevate the expression of adhesion molecules in eosinophils, such as integrins αM, β2, and β3.[39] The calcium-binding proteins S100A8 and S100A9 secreted from exosomes derived from nasal lavage fluid can facilitate the secretion of cytokines and chemokines, resulting in pro-inflammatory responses in monocytes and chemotaxis of immune cells.[35] In addition, S100A9 triggers the production of mucin protein MUC5AC and activates the nuclear factor-κB pathway in AECs, greatly contributing to mucin hyperproduction in the airway and exacerbating airway inflammation by inducing pro-inflammatory cytokines and chemokines.[40]

Conclusions

Different types of cells involved in asthmatic and allergic processes can secret exosomes that contribute to these pathologies (Figure 3). Therefore, it is necessary to investigate the exosomal load and composition and whether such a process depends on the cellular origins.[41] The exosomal miRNA profile is likely to reflect, in part, the cellular composition of the BALF because exosomes are cellular secretory products. Different cellular compositions of BALF between healthy controls and patients with asthma can result in distinct exosomal miRNAs as different cells produce different exosomes. Therefore, future investigations should assess the exosomal miRNA production by different cell types. Another important and clinically relevant question is whether exosomal miRNAs can reflect disease severity or acute exacerbation.

Not only the innate immune cells but also eosinophils play crucial roles in allergic and asthmatic processes. Two published studies have reported some important aspects of eosinophil exosomes in the pathogenesis of asthma.[14,39] Moreover, the secretion of exosomes is significantly higher in eosinophils from patients with asthma compared with healthy individuals.[14] Exosomes carry eosinophil-characteristic proteins such as MBP and EPO to BECs, ASMCs, and DCs, inducing secretion of mucus and inflammatory cytokines and chemokines, which results in tissue damage and exacerbation of asthma.

Xia et al.[31] showed that mast cells greatly contribute to the process of airway remodeling by stimulating the proliferation of ASMCs by exosomes. Mast cells can adhere to ASMCs via cell adhesion molecule 1 (CADM1) and trigger the secretion of cytokines and chemokines by ASMCs, resulting in the recruitment of more mast cells and perpetuating asthmatic symptoms. The release of exosomes from stimulated BECs can be induced by Th2 cytokines, principally IL-13, and these exosomes can trigger proliferation of monocytes, which contributes to inflammatory processes.[12]

Collectively, these findings indicate that exosomes exert a crucial function in communication between the asthmatic microenvironment and cells. This communication is two-way and even multi-directional.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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