Role of dendritic cell-derived exosomes in allergic rhinitis (Review)

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Abstract. Allergic rhinitis (AR) is a common pathological condition in otorhinolaryngology. Its prevalence has been increasing worldwide and is becoming a major burden to the world population. Dendritic cells (DCs) are typically activated and matured after capturing, phagocytosing, and processing allergens during the immunopathogenesis of AR. In addition, the process of DC activation and maturation is accompanied by the production of exosomes, which are cell-derived extracellular vesicles (EVs) that can carry proteins, lipids, nucleic acids, and other cargoes involved in intercellular communication and material transfer. In particular, DC-derived exosomes (Dex) can participate in allergic immune responses, where the biological substances carried by them can have potentially important implications for both the pathogenesis and treatment of AR. Dex can also be exploited to carry anti-allergy agents to effectively treat AR. This provides a novel method to explore the pathogenesis of and treatment strategies for AR further. Therefore, the present review focuses on the origin, composition, function, and biological characteristics of DCs, exosomes, and Dex, in addition to the possible relationship between Dex and AR.

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Contents

1. Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease of the nasal mucosa mediated by immunoglobulin E (IgE) (1). Dendritic cells (DCs), which are a major subtype of antigen-presenting cells (APCs), serve a key role in the immunopathogenesis of AR (1,2). When allergens enter the body, they are presented by DCs to CD4 T cells to trigger allergic inflammatory responses, leading to the activation and maturation of DCs (2,3). Exosomes are secreted during the maturation and differentiation of DCs in AR (4,5). However, almost all cells and not only DCs can produce exosomes (5-8). Exosomes are cell-derived, nm-sized extracellular vesicles (EVs) that are formed through the endocytosis and inward budding of the endosomal membrane mediated by extracellular components and cell surface proteins. They are distributed in almost all bodily fluids and have been previously associated with the occurrence and progression of several diseases (9,10). Exosomes can carry important signaling molecules for intercellular communication and material transfer (11). DC-derived exosomes (Dex) are nano-scale lipid-membrane vesicles formed within DCs by the inward budding of the endosomal membrane after DCs receive immune signals (12,13). The composition and function of DCs and Dex are strikingly similar. Dex, which mimics the biology of donor DCs, can transfer functional major histocompatibility complexes (MHC) to DCs, leading to the activation of CD8 and CD4 T cells (14-16). In addition, Dex carry MHC and T-cell costimulatory molecules to present allergens to induce the production of Th2 cytokines in allergic donors,

which are important immunostimulatory factors of anaphylactic immune responses (17,18). Therefore, allergen-carrying Dex may be important targets for AR immunotherapy (17,18). Since the diverse and complex mode of information transfer between Dex and various cells may serve an integral role in the occurrence and progression of AR, Dex engineered to carry anti-allergic drugs may have the potential to interrupt the allergic and immune processes underlying AR on a novel level (5,19).

2. Origin and function of DCs

DCs are a class of bone marrow-derived cells that are typically found in blood, tissues, and lymphoid organs. They primarily initiate immune responses by presenting antigens to naive T cells in lymphoid tissues (20,21). Once activated, DCs increase the expression levels of the MHC peptide complex and costimulatory molecules, allowing them to efficiently activate T cells (22). As the most efficient type of APCs, DCs serve a central role in the immune system. They are typically classified according to their location, function, and cell surface marker profile, namely plasmacytoid DCs (pDCs) and conventional DCs (cDCs; Fig. 1) (20,23-25). DCs can develop from different hematopoietic or myelopoietic progenitors, where to the best of our knowledge, no interconversion from one type to another has been found to date (26).

pDCs are also known as 'lymphoid DCs' and form a subset of DCs with antigen-presenting potential, accounting for <0.3% of all blood mononuclear cells (27,28). Although they share a similar origin with cDCs, pDCs have a different life cycle, since they primarily accumulate in the blood and lymphoid tissues, entering lymph nodes through the blood circulation (29). pDCs can develop *in situ* in the bone marrow or from common lymphoid progenitors (CLPs; Fig. 1) (24,30). They acquire the functions of APCs after activation, where their expression combination of costimulatory molecules CD40, CD80, and/or CD86 can dictate which specific T cell function is activated (24,31). After recognizing foreign nucleic acids, pDCs will produce large quantities of IFN-I and acquire the ability to present foreign antigens, which serve an important role in antiviral immunity (29,30). In addition, pDCs can directly inhibit allergic immune responses in the airway in addition to indirectly promoting the induction of regulatory T (Treg) cells in mice (32,33).

The majority of cDCs are short-lived hematopoietic cells that are constantly replaced by blood-derived precursors (29). cDCs account for a much larger proportion of DCs compared with pDCs and are typically distributed in most lymphoid tissues and non-lymphoid tissues. With highly efficient antigen-presenting ability, they can capture relevant antigens and present them to T lymphocytes after intracellular processing (29). Serving the role of 'sentinels', cDCs can respond to environmental stimuli and alert the immune system to the presence of foreign antigens, including allergens. cDCs have been reported to be required for the initiation of Th2 immune responses (24,32). Allergens can either signal directly through specific receptors on cDCs or indirectly by inducing cytokine production in surrounding tissues or inflammatory cells, which can then compel cDCs into promoting Th2 responses (32).

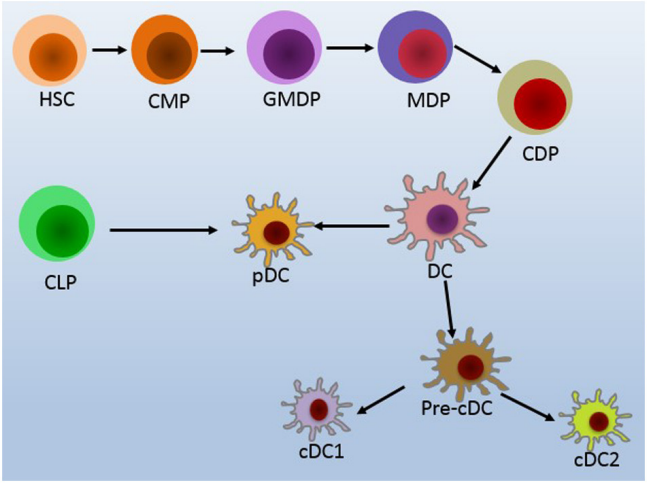

Figure 1. Origin and differentiation process of DCs. Cell potential descends from the apex through successive bifurcations, with each progenitor cell population having a homogeneous differentiation potential (20). DCs, dendritic cells; HSC, hematopoietic stem cell; CMP, common myeloid progenitor; GMDP, granulocyte-macrophage DC progenitor; MDP, macrophage DC progenitor; CDP, common DC precursor; CLP, common lymphoid progenitor; pDC, plasmacytoid DCs; cDC, conventional DC.

DCs in different types of tissues appear to serve different cellular functions, where various stimuli can induce the maturation of specific and distinct DC phenotypes that mediate different functions (34). However, during the resting state, when the DCs are immature (imDCs), they can acquire self-antigens but do not activate T cells. After being stimulated by injury, pathogens, or inflammatory cytokines, imDCs are then transformed into mature DCs (mDCs), which then migrate to secondary lymphoid tissues, where they prime naive T cells into initiating adaptive immune responses (35,36). In particular, only viable, mature, and fully functional DCs migrating into lymph nodes can stimulate T-cell responses (35). The maturation of DCs is accompanied by the enhanced expression of MHC II, costimulatory molecules, and chemokine receptors (37). It is mainly during the maturation of DCs that exosomes are produced.

3. Exosomes

Exosome biogenesis, release, and composition. Exosomes are EVs with lipid bilayer structures formed by extracellular components together with proteins, lipids, metabolites, small molecules, ions, and other liquids through the endocytosis and inward budding of the plasma membrane (9,38). The inward budding of the plasma membrane then forms early-sorting endosomes (ESEs) in association with the trans-Golgi network, mitochondria, and endoplasmic reticulum. These mature ESEs subsequently form late-sorting endosomes (LSEs) under the control of the endocytosis-sorting complex and other related proteins. After the specific sorting and encapsulation of proteins, lipids, and nucleic acids, LSEs then form multiple intraluminal vesicles (ILVs) through a second indentation. This process allows for the entry of cytoplasmic components into the newly formed ILVs, which are the precursors of exosomes (6,9,39,40). This sequential invagination of the plasma membrane eventually leads to the development of

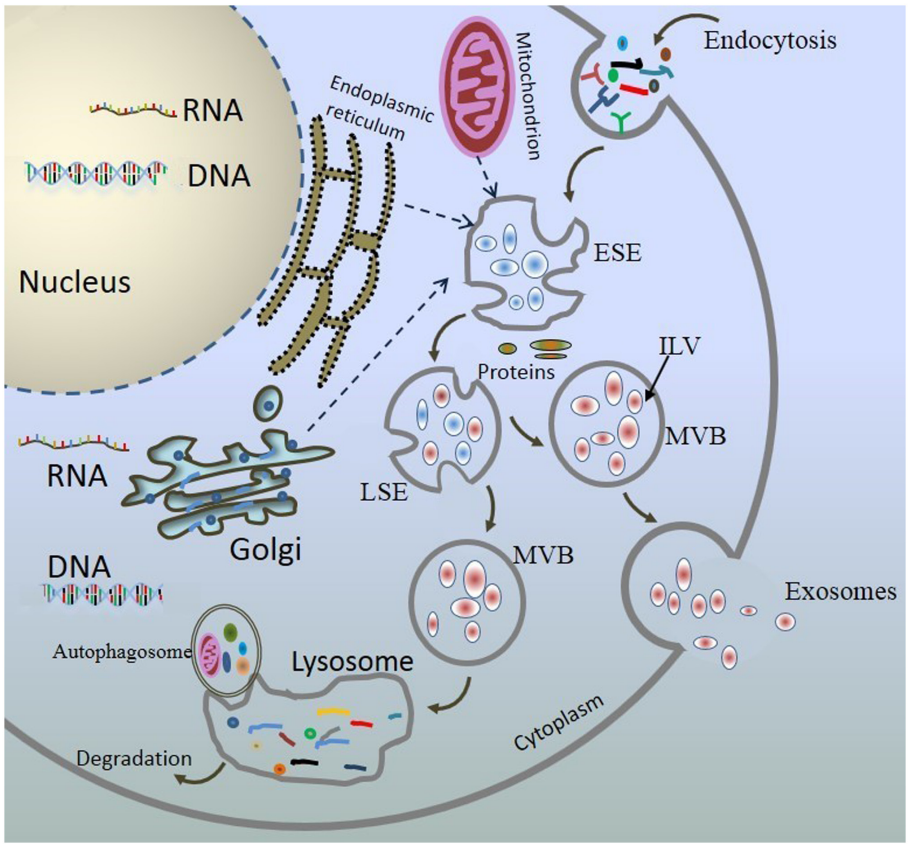

Figure 2. Biogenesis of exosomes. During the formation of exosomes, cargoes in the cytoplasm can enter the exosomes, which then transmit information among cells. ESE, early-sorting endosome; LSE, late-sorting endosome; ILV, intraluminal vesicle; MVB, multivesicular body.

multiple ILVs into multivesicular bodies. They can either fuse with lysosomes or autophagosomes for degradation or fuse with the plasma membrane to release the vesicles out of the cell through extravasation (Fig. 2) (41-44).

Exosomes contain a variety of components, including lipids, proteins, amino acids, metabolites, RNA, and DNA. The majority of these components can exert biological functions and define the transport capacity of the exosome (45,46). Proteins that are commonly found in exosomes include transmembrane proteins CD9, CD63, CD81, CD82, CD151, Ras-related proteins, immunomodulatory proteins, heat shock proteins (HSP), cell type-specific molecules, proteases, MHC molecules, tumor susceptibility gene 101 protein, apoptosis-linked gene 2-interacting protein X, integrins, and flotillin. They can be found on the surfaces, in between lipid bilayers, or within exosomes, with the yield of protein content from exosomes dependent on the type of cells that secreted them (9,47,48). Lipids form another important component that makes up the exosomes. They not only contribute to their support structures but are also important participants in their formation and release into the extracellular environment (49,50). Major lipid components of exosomes include sphingomyelin (SM), phosphatidylserine (PS), phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol (PI), phosphatidic acid, and cholesterol (Table I). The distribution of lipids in the exosome bilayer is typically asymmetric, where SM is primarily located in the outer layer, whilst PS is largely distributed in the inner layer (Fig. 3) (49-51).

However, it is important to note that exosomes from different sources can contain different ingredients, even if they originated from the same cell. As such, exosomal contents mostly likely depend on the status of the cell from which they were produced (8,45,48). They may vary under different physiological or pathological conditions, where changes in the external environment (such as various modes of stress, hypoxia, and inflammation) will influence the molecular profile of exosomes (46,57). The different molecular compositions of exosomes will likely have an impact on their transport capacity and messaging function.

Biological functions of exosomes. Exosomes were initially considered to be carriers of waste products from intracellular metabolism (66). However, subsequent studies have revealed that exosomes can serve to not only remove waste products of metabolism from the cell but also perform a variety of functions, such as intercellular communication, transport of intracellular, extracellular substances, and genetic material, as well as maintenance of cellular stability and removing cellular debris (67-70). In addition, exosomes can regulate innate and adaptive immune responses, specifically in antigen presentation and intercellular signaling. Akin to 'communicators', exosomes can serve as intercellular immune mediators regulating cell proliferation, differentiation, and migration, allowing them to mature and adapt rapidly to environmental changes (71,72). Although the biological functions of exosomes can vary depending on their origin, they have important reported roles in cell differentiation, maturation,

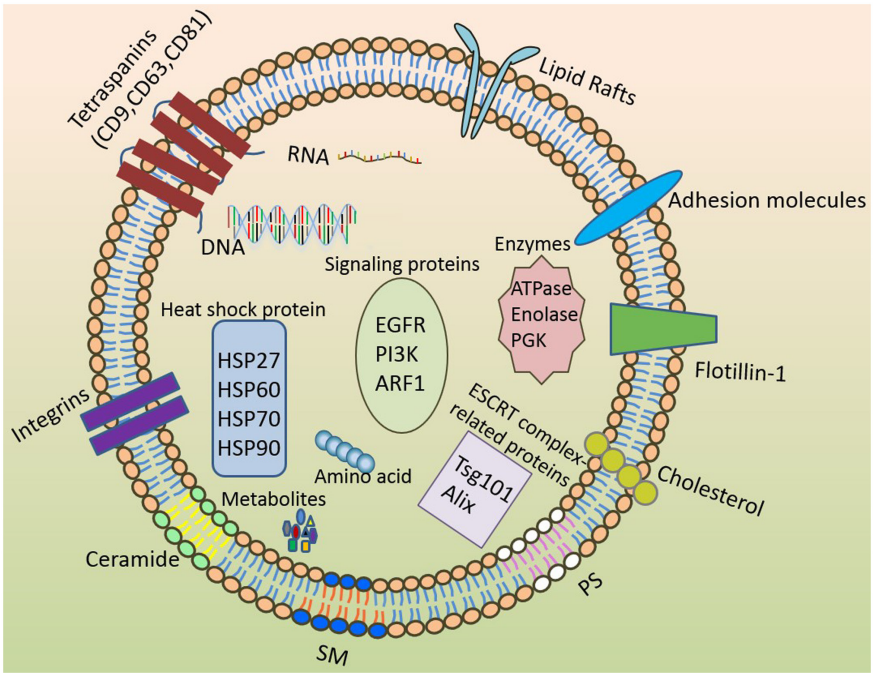

Figure 3. Schematic diagram of the exosome structure. Exosomes from different origins can contain different components. Substances that are commonly found in exosomes are shown in this figure. HSP, heat shock protein; TSG101, tumor susceptibility gene 101; ALIX, apoptosis-linked gene 2-interacting protein X; PS, phosphatidylserine; SM, sphingomyelin; ARF1, ADP-ribosylation factor 1; PGK, phosphoglycerate kinase.

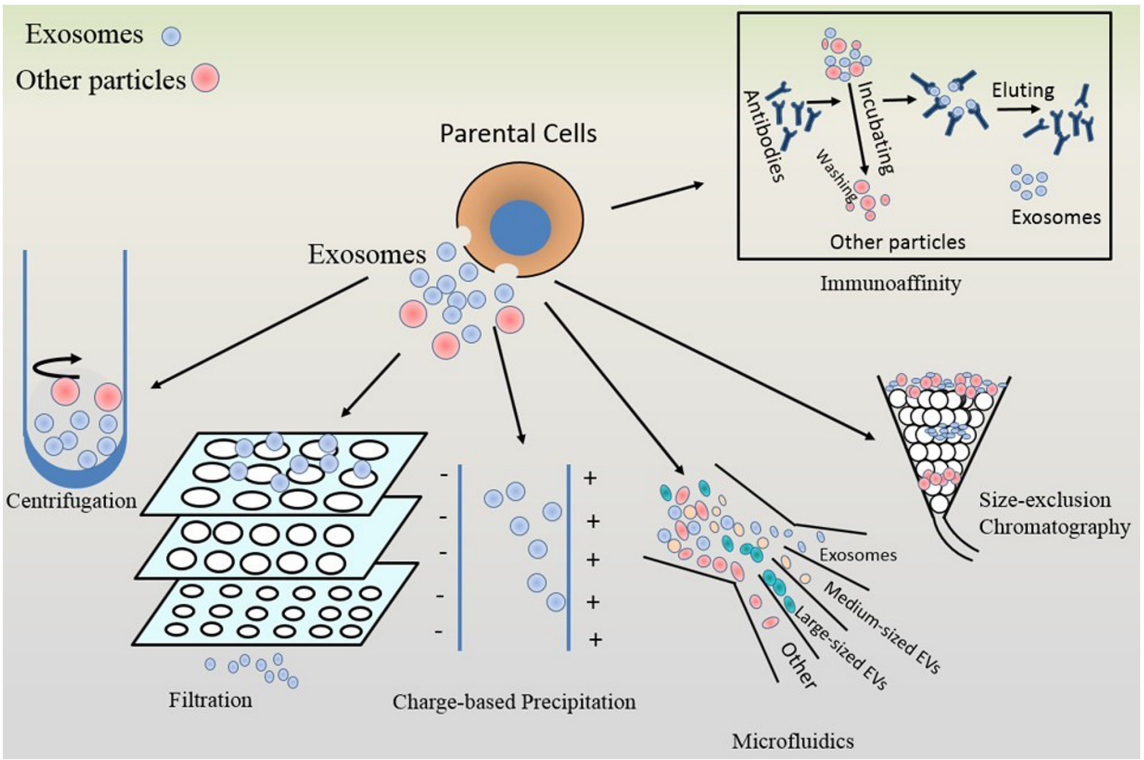

Figure 4. Summary of common methods used for exosome isolation. EVs, extracellular vesicles.

and apoptosis (8,73). The core functions of exosomes are mainly determined by the proteins, lipids, and nucleic acids contained within their parental cells (73).

Exosome isolation and purification methods. Exosomes with multiple biological functions can be used for the diagnosis, treatment and prognostic evaluation of numerous diseases such as cardiovascular disease, neurodegenerative diseases, and HIV (74,75). Efficient and high purity but simple methods for exosome isolation and purification form the first step for optimizing the field of exosome research (74). Over the past decade, rapid progress has been made in the study of exosomes.

Table I. Primary components within exosomes[a].

Composition	Type	Content	(Refs.)
Protein	Ras-related proteins	Rab GTPase, Annexins, Syntenin-1, TSG101, ALIX, Syndecan-1, endosomal sorting complexes required for transport proteins	(9,10,46,52,53)
	Exosomes surface proteins	Tetraspanins, integrins, immunomodulatory proteins, membrane transport proteins, surface proteoglycans, antigen presentation proteins, epithelial cell adhesion molecule, epidermal growth factor receptor, insulin-like growth factor receptor 1	(9,54)
	Intracellular proteins	Cytoskeletal proteins, HSPs 27, 60, 70 and 90, nuclear proteins, enzymes, RNA-binding proteins, apoptotic proteins, signal transducers	(9,10,54,55)
	Markers for exosomes	CD9, CD63, CD81, CD82, CD151, flotillin, TSG101, ALIX	(9,10,47,52,54)
	Others	Hemoglobin, histones, actins, tubulins, inter-α-trypsin inhibitor, gelsolin, talin 1, WD repeat domain 1	(53)
Nucleic acid	RNA	mRNA, microRNA, pre-RNA, Y-RNA, circular RNA, long non-coding RNA, transfer RNA, mtRNA, transfer RNA-derived small RNAs, small nucleolar RNAs, Piwi-interacting RNA	(9,10,43,46, 53,54,56-60)
	DNA	mtDNA, double-stranded DNA, single-stranded DNA, viral DNA, genomic DNA, cell free DNA	(9,53,54,56)
Lipid	N/A	Sphingomyelin, phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatodylcholine, phosphatidylethanolamine, ceramide, cholesterol, Cardiolipin, diglyceride, monoglyceride, phosphatidylglycerol, triglyceride	(10,43,50,53)
Amino acids	N/A	Valine, isoleucine, phenylalanine, tyrosine, homocysteine, cystine	(52,61,62)
Metabolites	N/A	Lipid fatty acids, benzene, organic acids, carbohydrates, fatty acyls, carnitines, biogenic amines, vitamins	(9,10,63,64)
Glycans	N/A	Polylactosamine, high mannose N-glycan, complex type N-glycan	(53,65)

[a]According to previous reports, 4,563 proteins, 194 lipids, 1,639 mRNAs, 764 miRNAs and 196 metabolites were found in exosomes. Amongst this list, syntenin-1 appears to be the most abundant protein, whilst organic acids and their derivatives and fatty acids are the most abundant metabolites in exosomes of different origins (52,55,63). TSG101, tumor susceptibility gene 101; ALIX, apoptosis-linked gene 2-interacting protein X; HSP, heat shock proteins; mtRNA, mitochondrial RNA; miR/miRNA, microRNA.

However, several outstanding obstacles must be overcome, such as cumbersome separation methods, low speed, low yield, and purity (76). Common exosome isolation and purification methods include ultracentrifugation, ultrafiltration, precipitation, immunoaffinity capture, and volume exclusion chromatography (75). All these aforementioned methods share similar disadvantages (Fig. 4; Table II). As this field develops, emerging methods for exosome isolation and purification are currently being found, such as microfluidics, electricity, centrifugal force, and acoustic force, which can be exploited to isolate exosomes of high purity in a high-throughput manner (Fig. 4; Table II) (74).

4. Composition and features of Dex

Dex are nm-sized vesicles formed within the cell by the inward budding of the endosomal membrane (12). There are a variety of proteins in Dex, such as integrin α and β chains (αMβ2), immunoglobulin family member intercellular adhesion molecule (ICAM), and milk fat globule epidermal growth factor 8 (MFG-E8), cytoskeleton proteins and anti-apoptosis-related proteins, which dock their membranes onto those of host cells. CD9, CD63, and CD81 are also components that are frequently found on the Dex surface membrane (83-85). The composition of Dex membranes differs from those of DCs in that they are richer in sphingolipid content but poorer in phosphatidylcholine content, in addition to being deprived of cholesterol (13). The lipid composition of Dex membranes can have an impact on their function (86). HSP70, HSP90, and heat shock cognate protein 73 have also been found in Dex, which can increase the immunogenicity of Dex (87). There is also a variety of different types of RNAs in Dex, which can transfer onto other cells. In particular, Dex has been documented to contain several immunomodulatory molecules with different structures and biochemical properties, depending on the intracellular origin of Dex (88). The composition and features of Dex are shown in Table III.

5. DCs and Dex

DCs can secrete different types of exosomes to regulate the adaptive immune response. In addition, exosomes from different sources can modulate the differentiation, maturation, and function of DCs (77). Dex, in addition to the known immunostimulatory capabilities of DCs, has been reported to regulate a variety of immune processes, including antigen

Table II. Comparison of methods used for the extraction of exosomes[a].

Methods	Advantages	Disadvantages	(Refs.)
Ultracentrifugation	Most commonly used, wide range of applications, low cost	Low quantity, low recovery, low purity, costly instrumentation, lengthy and laborious processing, requirement for large amounts of samples	(43,46,54, 77-79)
Density gradient centrifugation	Easy implementation, high practicability, high purity	Time consuming, dependability	(43,46,54,78)
Filtration	Uniform size	Possible blockages, low recovery	(43,46,54,80)
Co-precipitation	Simple, fast, reproducibility, high yield	Low quality, lack of specificity	(43,46,54)
Immunoaffinity enrichment	High purity, simple	Narrow range of applications, not applicable to large scale, high cost, low yield	(43,46,54)
Field flow fractionation	Wide range of separation, wide variety	Time consuming, requirement for specialized equipment	(43,46)
Asymmetric-flow field-flow fractionation	Efficient, high reproducible, fast, simple, label-free, gentle	Low resolution, possible irreproducibility	(53,80)
Contact-free sorting	Fast and easy to operate, label-free, high separation yield and resolution	Requirement for specialized system	(81)
Ultrafast-isolation system	Remove small particles, enhanced speed, yield, and purity	Requirement for specialized system	(77)
Size-exclusion chromatography	High yield, low cost, reproducibility, no damage, high recovery	Complex	(43,54,79,82)
Microfluidics-based techniques	Low cost, efficient, high speed, accuracy	Equipment complexity, difficult to operate	(54)
Membrane-based separation	High purity, fast	May contain other impurities with membrane	(74)
Commercial kit	Easy to operate, time saving	Expensive, uneven extraction	(6,74)

[a]Exosomes can be isolated and purified using other methods not shown in this Table. Different isolation and purification methods can complement each other and/or be used in combination to obtain more comprehensive information about exosomes.

presentation, immunomodulation, and signal transduction (12,92). With the ability to activate naive T-cells and facilitate the transfer of MHC complexes between DCs, Dex can be produced in large quantities and efficiently diffuse into tissues, rendering them potentially more potent compared with DCs in activating T lymphocytes and natural killer cells (93-95). The immunomodulatory effect of Dex is closely associated with the maturation status of DCs (96). imDCs and mDCs secrete exosomes with similar morphology, where the potency of exosomes secreted by mDCs is substantially higher compared with that of exosomes from imDCs (97). In general, exosomes from mDCs (mDex) have higher levels of immune-related molecules and superior antigen presentation compared with those from imDCs, which are prone to exosome production but do not effectively stimulate T-cell responses (84,93,94,97).

Dex can transfer MHC I and II complexes to DCs to amplify the immune response (84,98). LPS has been found to promote Dex production from DCs, which contain high concentrations of MHC molecules (86). In addition, Dex has been reported to stimulate T-cells and enhance their activity, thereby potentiating the immune response (86). The shuttling of miRNAs between DCs using Dex can serve as a means of communication and post-transcriptional modification, which may regulate the overall function of DCs (87). Rao *et al* (99) previously found that Dex can selectively enter DCs, since they have a high affinity for DCs and can act on them to alter the distribution and differentiation of T-cells by encapsulating triptolide. In another previous study, Zhang *et al* (100) found that Dex contains cargoes secreted by DCs that can activate Treg cells, which leads to the improvement of inflammation. However, it is important to note that Dex from different subsets of DCs may mediate different functions, ultimately leading to different downstream outcomes (14).

6. Dex and AR

DCs have been extensively reported to be involved in the pathogenesis of AR. Therefore, it is highly likely that Dex will play a potentially important role in AR. Dex can be recaptured by DCs and remain on the cell surface, where they can present allergens and induce Th2 cytokine production in allergic donors to elicit allergic immune responses (18,101).

Table III. Primary components of Dex.

Composition	Contain	Features	(Refs.)
MHC-peptide complexes	MHC I, MHC II	Initiate antigen-specific CD4 and CD8 T cells, modulate the function of T cells, enhance the ability of antigen presentation, trigger effective antigen-specific immune response	(54,89)
Costimulatory molecules	CD80, CD86, CD40	Initiate and activate T cells	(12,90)
RNA	microRNA, mRNA	Regulate the expression levels of relevant genes, post-translational modification, post-transcriptional regulation, communication between DCs, transport function	(12,13, 54,85)
Integrins	α and β chains	Target to recipient cells	(89)
Intercellular adhesion molecule 1	Immunoglobulin family member	Target and dock to recipient cells, activate DCs and increase the number of CD8 T cells, Increase the combination of Dex and APC, induce cell migration	(54,57, 89)
Milk fat globule epidermal growth factor 8	Immunoglobulin family member	Target and dock to recipient cells, bind phosphatidylserine on Dex's outer membrane, link integrins to promote Dex uptake, enhanced APC uptake of Dex	(12,85)
Lipid	Sphingomyelin, phosphatidylinositol, diaglyceride, phospholipids, phosphatidylethanolamine	Stability in the circulation	(13,85, 91)
Tetraspanins	CD9, CD37, CD63, CD81, CD82	Abundantly expressed in the surface membrane of Dex, contribute to Dex-targeted APC	(85)
Heat shock proteins	HSP70, HSP90	Assist MHC molecules to load antigens, Enhance Dex immunogenicity, promote the activation of natural killer cells and enhance their cytotoxicity	(12,54, 85)
Cytoskeletal proteins	Tubulin, actin, actin-binding protein	Cytoskeleton	(85)
Membrane transport and fusion proteins	Annexins, RAB proteins	Transport function	(85)
Anti-apoptosis related proteins	Thioredoxin peroxidase II, apoptosis-linked gene 2-interacting protein X, galectin-3	Resist apoptosis	(85)
Signal transduction pathways proteins	G proteins, kinases	Involve in signal transduction	(12,85)

Dex, dendritic cell-derived exosome; MHC, major histocompatibility complex; DCs, dendritic cells; APCs, antigen-presenting cells; HSP, heat shock protein.

Dex share similarities with DCs in promoting allergic immune responses (102). Dex can present antigens directly to T-cells or transport MHC complexes back to the surfaces of DCs for presentation to T-cells after docking onto APCs (103). CD40 on Dex has been found to induce T-cell responses to promote IgE production (104-106). In addition, CD63 and CD81 in Dex have been shown to inhibit FcεRI-induced degranulation by mast cells (MCs), which further affects signaling that normally mediates allergic inflammation (107). Costimulatory molecules, such as CD80 and CD86, on the Dex surface can also contribute to the maturation of DCs and promote Th2-type inflammation, leading to an imbalance in the differentiation of naive T-cells towards to Th2 subtype (108). In addition, CD80 and CD86 can activate allergen-specific Th2 cells to potentiate antigen-specific immune responses (109,110). By contrast, miRNAs in Dex can regulate serum IgE levels and the severity of allergy symptoms through blood, nasal mucosa, and nasal secretions in AR (111). Therefore, miRNA cargoes in Dex can be used to determine the extent of allergic inflammation and immune response (106). Changes in the expression levels of ICAM and MFG-E8 can also regulate the immune response (112). SM can drive allergic inflammation and promote airway hyperresponsiveness by serving as important signaling molecules for mediating inflammatory and immune

responses (113-115). This suggests that a wide variety of cargoes carried by Dex can mediate an impact on AR, though different cargoes are likely to exert different effects on AR.

The immunostimulatory or suppressive function of Dex is dependent on the type or maturity stage of DCs that secrete them (116). Therefore, Dex in different states is also likely to have different effects on AR. Exosomes from imDCs (imDex), which primarily reduce T-cell-dependent immune activation, contribute to inhibiting the Th17 response whilst enhancing the population of Treg cells (15,117). By contrast, mDex can directly act on T-cells to exert specific immune responses (118). By functioning as an antigen-presenting molecule, Dex can modulate immunity and inflammation by perpetuating the response of Th2 cells to DCs (119). Dex carries leukotriene synthase, which stimulates granulocyte translocation to promote the recruitment and migration of immune cells to sites of inflammation (77,110,120). Choi *et al* (121) previously showed that DCs can excrete allergen-bound Dex, which can trigger the degranulation of adjacent MCs, leading to anaphylaxis. Furthermore, DCs have been reported to secrete TNF-α and other proinflammatory cytokines in response to Dex stimulation, leading to increased inflammation (122). In another study, Huang *et al* (123) activated DCs using thymic stromal lymphopoietin (TSLP), which induced Dex release and in turn promoted the proliferation and differentiation of $CD4^+$ T-cells into the Th2 subtype through the OX40 ligand. These studies suggest that Dex can serve a significant role in the pathogenesis of AR through different types of cargo.

It is noteworthy that Dex can not only aggravate allergic reactions but also prevent them. Exosome-mediated transfer of allergens can promote allergic inflammation whereas regulatory and/or tolerogenic exosomes can suppress allergic and hypersensitivity reactions (19). Immunotherapy using Dex typically involves loading antigens directly into Dex or by modifying them (122). DCs can be modified to produce immunosuppressive Dex for the treatment of allergic inflammation (19). Dex can also be modified to carry anti-allergic drugs that can reduce allergic airway inflammation. In addition, lipids and proteins carried by Dex can enhance the permeability of biological membranes, which facilitates the efficiency of the delivery of the anti-allergic drugs they carry (19,124,125). In particular, mDex can promote the activation of T and B cells, leading to Th1-type immune responses and increased IgG titers (101). Since high IgG titers inhibit IgE-mediated effector function, it also suppresses the allergic inflammation that causes AR (101). In addition, imDCs treated with IL-10 and IL-4 have been reported to produce tolerogenic Dex to attenuate Th2 cell responses, thereby inhibiting inflammatory responses, in a mice model of delayed-type hypersensitivity (DTH) (84,126). The inhibitory capacity of IL-10-treated imDCs depends on the presence of CD80 and CD86 (127). Bianco *et al* (128) previously revealed that Dex overexpressing indoleamine 2,3-dioxygenase has anti-inflammatory effects in a mouse model of DTH, which are dependent on the costimulatory molecule B7. Furthermore, Jia *et al* (129) showed that DCs-derived forkhead box p3-exosomes inhibited the proliferation of $CD4^+$T cells, which in turn reduced the population of Th1 and Th17 cells whilst increasing that of Treg cells without affecting the level of Th2 cells. In another previous study, Yu *et al* (130) found that Dex modified with IL-2 can upregulate Treg differentiation to suppress allergic inflammation. Kim *et al* (131) also showed that genetically modified Dex derived from FasL-expressing DCs can exert anti-inflammatory and immunosuppressive effects by suppressing DTH in an antigen-specific and MHC-II-dependent manner, though this process was independent of MHC I. These aforementioned findings suggest that Dex can either be processed or modified to inhibit allergic inflammation and thereby treat AR. Since Dex as a candidate for the treatment of AR is less susceptible to the effects of the surrounding environment (132), these findings could inspire further exploration into novel methods for treating AR with Dex.

Dex, with superior biocompatibility, biodegradability, and safety, can activate various immune cells and hold significant advantages in terms of delivery efficiency (85). Dex is more stable, can be stored for longer, and more immunogenic than DCs, which are highly susceptible to external factors that induce their maturation under pro-inflammatory conditions and promote immune responses, in addition to inducing their tolerance and moderate immune responses in response to IL-10 and TGF-β stimulation (85,133). These advantages of Dex suggest their viability for the treatment of AR. Treating AR with Dex not only eliminates the need for direct contact with natural allergens but is also less prone to triggering IgE/MC reactions. Therefore, they tend to be safer and more effective for the treatment of AR (19). The feasibility and safety of Dex therapy has the potential to be one of the alternatives to conventional treatments of AR (110). It is encouraging that Dex-based therapies are already in clinical trials (101). However, the scope of clinical trials for Dex is limited compared to DC vaccines, where their potential for application has not been fully evaluated (122). The role of exosomal vaccines is dependent on the environment, antigen, and cell type (122), which will require more in-depth research in the future.

7. Conclusions and future perspectives

From the aforementioned studies, it is likely that Dex is involved in the pathogenesis and can be exploited for the diagnosis and treatment of AR. However, their roles can vary during the different stages of AR. The role of Dex in AR opens another door to understanding the pathogenesis of AR, furthering the potential to design interventions and/or sensitizations to the immunotherapy of AR on a novel level. Although rapid progress has been made in the understanding of Dex (12), the clinical exploitation of Dex remains hindered by a series of problems, such as low efficiency, poor yields, difficulty associated with expression, and low purity (10,122). In addition, research on Dex biomarkers or targeted therapies for AR remains in the early stages and requires further development (77). The complexity of Dex requires thorough understanding. In addition, it remains necessary to carefully monitor the potential adverse events associated with Dex in future trials (12). Therefore, the role of Dex in AR will need to be enhanced further with a specific focus on the problems currently obstructing progress to adequately refine and improve the application of Dex in AR therapy. It is hoped that Dex can be used as an important marker for the diagnosis, treatment, and prognosis of patients with AR in the future,

which requires more in-depth research on the isolation and purification, sensitivity, and cost-effectiveness of Dex. In addition, a more thorough exploration into the composition and mechanism of action mediated by the various cargoes contained within Dex needs to be performed.

Is it possible to adjust or change the composition and function of Dex as needed to diagnose or treat AR? It is possible to design Dex to stimulate or inhibit immune responses as needed? Can Dex be a candidate for the treatment of AR? How can Dex be produced for the personalized clinical diagnosis and treatment of AR according to the situation? These questions need to be addressed in future studies. A more thorough understanding of the role of Dex in AR could help prevent AR or develop more effective treatment strategies. This provides a novel insight for exploration into the pathogenesis of AR and offers a new direction for the efficient treatment of AR.

Overall, the application of Dex in the diagnosis and treatment of AR is a promising approach, where novel insights in this field will drive the development of new therapeutic or preventive measures. However, the role of Dex in AR warrants further investigation in the future.

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Availability of data and materials

Not applicable.

Authors' contributions

CK and HH conceived and drafted the manuscript. CK, HH, JL, SQ, PL, YL, XL, JZ, HR, XZ, and HZ reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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