Review

The potential of exosomes in allergy immunotherapy

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Abstract: Allergic diseases represent a global health and economic burden of increasing significance. The lack of disease-modifying therapies besides specific allergen immunotherapy (AIT) which is not available for all types of allergies, necessitates the study of novel therapeutic approaches. Exosomes are small endosome-derived vesicles delivering cargo between cells and thus allowing inter-cellular communication. Since immune cells make use of exosomes to boost, deviate, or suppress immune responses, exosomes are intriguing candidates for immunotherapy. Here, we review the role of exosomes in allergic sensitization and inflammation and we discuss the mechanisms by which exosomes could be used in immunotherapeutic approaches for the treatment of allergic diseases. We propose the following approaches: a) Mast cell derived exosomes expressing IgE receptor FcεRI could absorb IgE and down-regulate systemic IgE levels. b) Tolerogenic exosomes could suppress allergic immune responses via induction of regulatory T cells. c) Exosomes could promote TH1-like responses towards an allergen. d) Exosomes could modulate IgE-facilitated antigen presentation.

Keywords: Type I hypersensitivity; IgE; AIT; SIT; extracellular vesicles; vaccine

1. Allergy and allergy immunotherapy

Allergic diseases are a global issue as more and more people are affected by allergies [1]. Type I hypersensitivity is characterized by abnormal IgE-mediated inflammation in response to harmless antigens called allergens caused by a lack of immune tolerance coupled with expansion of TH2 cells that drive IgE responses from B cells [2], [3]. Allergen-specific IgE sensitizes mast cells and basophils by binding to the high-affinity IgE receptor FcεRI [4]. Upon secondary contact with the allergen, those cells degranulate and release inflammatory mediators [5]. Symptomatic treatment options for allergies involve down-regulation of the mediators released by mast cells or basophils (e.g anti-histamine) or aim to down-regulate IgE such as the monoclonal anti-IgE antibody Omalizumab [6]. The only disease modifying treatment available for some but not all allergies is allergen-specific immunotherpapy (short AIT or SIT). AIT is a repeated immunization approach that aims to re-educate the immune system and generate tolerance towards the allergen [7], [8]. Mechanistically, AIT induces regulatory T cells and B cells that act anti-inflammatory such as IL-10 and TGF-β. This leads to a suppression in TH2 responses but increased IgG4 production [9]–[11]. A novel approach in allergy immunotherapy is to boost immune responses by eliciting a non-allergic, but rather anti-viral/bacterial TH1-like response [12]. In general, it is accepted that IgG antibodies can suppress IgE-mediated effector functions by competing for the allergen epitope thus neutralizing IgE, or by ligation of inhibitory FcγRIIb receptors on mast cells/basophils [13]–[15]. FcγRIIb receptors contain immunoreceptor tyrosine-based inhibitory motif (ITIM) signaling domains that shut down FcεRI -dependent effector cell activation [16]–[18]. Additionally, FcγRs and IgG can promote the

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internalization of IgE thus preventing IgE-dependent activation of effector cells [19]. However, further research in this area is still required as IgG can also contribute to inflammation, depending on IgG subclass and type of FcγR receptor involved [20]–[22].

2. The Biology of Exosomes

The biology and biomedical application of exosomes are reviewed by Kalluri & LeBleu [23]. In brief, Extracellular vehicles (EVs) are small membrane blebs with a diameter of approximately 40nm-1μm released from cells. Exosomes (40-160nm) are of endosomal origin, which distinguishes them from ectosomes that are budding from the surface of plasma membranes. Because of this endosomal origin exosomes are enriched with endosomal-associated membrane proteins such as major histocompatibility complex (MHC) Class I and II and tetraspanin proteins e.g. CD63, CD81, CD82 which have been shown to be involved in cell activation, proliferation and antigen presentation [24]. To this end, EVs can provide the organisms with molecules such as transferring membrane material between different cells by fusing to target cells without the need of direct cell-cell contact. Furthermore, EVs can be loaded with cargo proteins and RNA [25]. Thus, EVs, specifically exosomes have been a fast-rising topic due to their relevance as communicators and modulators for the immune system. Exosome function is dysregulated in a variety of diseases and thus their therapeutic potential is intriguing [23]. This is also true in allergic diseases as EVs, specifically exosomes seem to play a role in the dysregulated communication in allergy and allergic asthma [5], [6].

3. Exosomes in the regulation of immune responses

The transfer of exosomes between immune cells can have a strong functional effect on immune responses and either promote, deviate or suppress immune responses [26]–[28]. Many studies have shown that dendritic cells modulate CD4+ as well as CD8+ immune responses via exosomes that carry MHCI or MHCII molecules as well as co-stimulatory molecules CD8/CD86 [29]–[31]. Interestingly, extracellular vesicles containing intact p-MHC complexes pre-loaded with antigen-derived peptide can also lead to direct antigen presentation without the need of antigen processing, this mechanism of antigen presentation is referred to as "cross-dressing" [32]–[34]. Besides exosomal transfer of p-MHCII and native antigens, RNA cargo provides a fundamental mechanism for intercellular communication [35]. Donor cells package mRNA or small non-coding micro RNAs (miRNAs) into exosomes. In the exosome-receiving cell, mRNAs can be translated into proteins and miRNAs can post-transcriptionally regulate target mRNAs. The transfer of miRNA exists in immune cells as means for antigen presenting cells (APCs) communication and activation [36]–[38]. Interestingly, viruses can highjack this system as EBV-infected B cells transfer viral miRNAs to DCs that silence immune-stimulatory molecules [39]. Regulatory T cells can suppress CD4+ T cell proliferation and cytokine production by transferring miRNA via exosomes which block gene expression [40], [41]. Mesenchymal stem cells (MSC) are of high interest in the treatment of inflammatory diseases as they produce anti-inflammatory exosomes that can suppress DC maturation, T cell activation and promote regulatory T cells and B cells [42]–[45]. Cancer cells use exosomes carrying tumor antigens or inhibitory molecules can suppress the activation of DCs, T cells and NK cells in the tumor microenvironment [46]–[48]. Due to all those immunomodulatory properties, exosomes have become a promising novel tool in immunotherapy [49]–[51].

4. Exosomes in allergic sensitization and inflammation

Exosomes play a role in a number of allergic processes that could potentially be manipulated for allergen specific immunotherapy [52]–[54]. Allergic sensitization is driven by barrier disruption skin or lung where inflammatory signals from epithelial cells, including thymic stromal lymphopoietin (TSLP)/IL-25/IL-33 are thought to activate type 2 innate lymphoid cells (ILC2) and thus a TH2 bias [55], [56]. Interestingly, it was shown that TSLP-activated DCs release OX40L expressing exosomes that drive CD4+ TH2 proliferation and differentiation [57]. In asthma, significant differences in 24 exosomal miRNAs were found

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in bronchoalveolar fluids (BAL) of allergic versus asthmatic patients [58]. The miRNA-17-92 cluster (miRNA-17-5p, miRNA-17-3p, miRNA-18a, miRNA-19a, miRNA-19b, miRNA-20a, and miRNA-92-1) was shown to be an important regulator of T cell biology [59] and among the different miRNAs in the cluster, miR-19 is upregulated in CD4+ T cells from asthmatic patients compared to healthy individuals [60]. Like the miR-17-92, the miR-23 cluster plays a role in T cell function and in particular in controlling TH2 differentiation by targeting IL-4 and GATA3 [61]. Upon allergen exposure, exosomes released from epithelial cells induce the proliferation and the chemotaxis of macrophages during asthmatic inflammation [62]. Recently, an interesting study showed that in epithelial exosomes, contactin-1 is involved activation a recruitment of monocyte-derived dendritic cells T-cell responses in allergic asthma [63]. Likewise, eosinophil-derived exosomes promote eosinophil migration, augment adhesion by a specific increase of adhesion molecules such as ICAM-1 and induce reactive oxygen species (ROS) and nitric oxide (NO) production in autocrine fashion [64]. Additionally, this leads to alveolar epithelial cell (AEC) death, to delay wound repair and to increase airway smooth muscle cell proliferation which causes airway obstruction and tissue remodeling [65]. Exosome production is also increased by airway allergen exposure as it was shown that PBMCs from House dust mite (HDM) allergic patients produce higher numbers of exosomes in response to HDM re-stimulation and HDM-induced exosomes were also shown to contain altered cargo/properties than exosomes produced in unstimulated PBMCs [66], [67]. An interesting report showed that DCs are able to package native cat allergen Fel d 1 into exosomes [68]. B cell derived exosomes were reported to carry processed birch allergen Bet V 5 peptide/MHCII complexes that can stimulate proliferation, IL-5, and IL-13 production from BET v 1 specific T cells lines [69].

5. Potential exosome-based therapeutic approaches in allergy immunotherapy

5. 1. The therapeutic potential of Mast cell derived exosomes

Mast cells (MC) are in many ways the quintessential cell in allergy and thus also of high interest in allergy immunotherapy [70]. MCs are located at barrier sites in skin, lung and gut and are involved in allergic sensitization, inflammation but also resolution and tolerance. MCs express the high affinity receptor for IgE, FcεRI which upon cross-linking of the FcεRI-bound IgE by allergen induce a signal pathway leading to release of preformed granules [70]. Likewise, MCs are a source of exosomes from endosomal compartment which are released by exocytosis of the cells and like other immune cells, MCs can shuttle MHC molecules, RNA and chaperones that are able to modulate immune responses [71]. It was reported that mast cell derived exosomes containing MiR103a-3p enhance IL-5 production from ILC2s [72]. Furthermore, MCs can promote TH2 immune responses by OX40L expressing exosomes that interact with OX40 on T cells. An interesting study suggested that MCs regulate their own differentiation via exosomes by communicating with blood CD34+ progenitor cells [74]. It was reported that mast cell derived exosomes can induce functional maturation of DCs for efficient antigen cross-presentation to T cells [73]. A specific interest for allergy immunotherapy is the fact that mast cell derived exosomes express FcεRI [71]. It was shown in an elegant study that mast cell-derived exosomes can neutralize IgE via surface displayed FcεRI [75]. As mentioned above, anti-IgE therapy is an established approach in the treatment of allergy [76]. Using IgE-neutralizing mast cell derived exosomes that reduce systemic IgE levels and thus down-regulate systemic allergic sensitization could be a novel approach (Figure 1). Alternatively, FcεRI could also be engineered to be expressed on exosomes from other cell types than mast cells.

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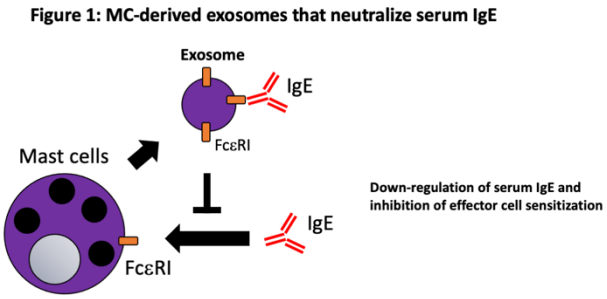

Figure 1: Mast cell (MC)-derived exosomes that neutralize serum IgE
MC-derived exosomes or exosomes engineered to express FcεRI could be used to down-regulate serum IgE levels and inhibit binding to FcεRI on MCs or basophils thus reducing allergic sensitization.

5.2 "Tolerosomes" for the suppression of allergic TH2 responses

A key concept of allergy immunotherapy is the generation of tolerance towards the allergen [77]. Tolerance-inducing exosomes also referred to as "tolerosomes" can be produced by gut epithelial cells and promote regulatory T cells and can suppress immune responses in MHC dependent fashion [78], [79]. It was demonstrated that OVA-fed mice display elevated levels of serum tolerosomes that suppress allergic sensitization and protect from allergic asthma in a murine model [80]. Another interesting study showed that Exosomes isolated from BAL fluid of tolerized donor mice suppress allergic inflammation in recipient mice by promote allergen-specific regulatory T cells that can suppress immune responses altogether thus limiting the production of IgE and airway inflammation [81]. MSC-derived exosomes have been shown to promote tolerogenic DCs by reducing maturation and production of inflammatory cytokines [45]. This concept was also confirmed in allergy as MSC-derived exosomes suppress allergic rhinitis in a murine model and human MSC-derived exosomes suppress Th2 differentiation via the miR-146a-5p/SERPINB2 axis [44], [82]. In a different study it was shown that MSC-derived exosomes alleviate atopic dermatitis [83]. Interestingly, regulatory DCs stimulated with IL-2 and antigen produce exosomes carrying IL-2 and p-MHCII complexes which promote Tregs and suppress allergic inflammation in a murine model of food allergy [84]. This concept fits into the strategy of expanding of T regs via IL-2, which has been a promising and fast-evolving field, including in allergy immunotherapy [85], [86]. It is generally accepted that T reg released IL-10 and TGF−β is important for the establishment of allergen tolerance [87]. Additionally, Tregs themselves have been reported to suppress immune responses via exosomes which could be applied in similar fashion [40], [41]. Hence, exosomes from tolerogenic DCs, MSCs or T regs could be used for the inductions T regs and tolerance in allergy immunotherapy (Figure 2).

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Figure 2: Tolerosomes derived from DCs, IEC or MSC to induce allergen tolerance via Tregs

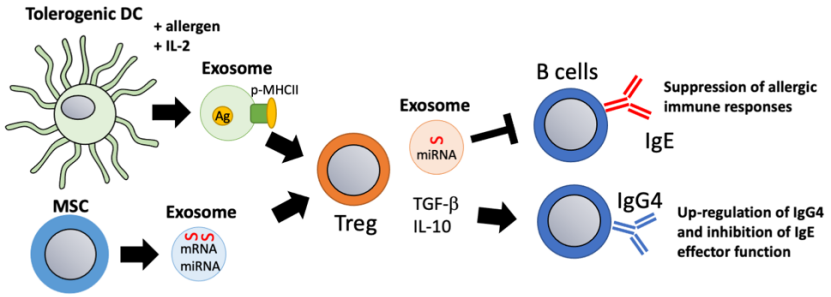

Figure 2: Tolerosomes derived from DCs, IEC or MSC to induce allergen tolerance via Tregs

Exosomes derived from IL-2 primed tolerogenic DCs or from MSCs promoting regulatory T cells could be used to suppress TH2 responses. Alternatively, Treg-derived exosomes themselves could be harnessed to suppress TH2 responses.

5.3 Exosomes as a vaccination approach to boost TH1 responses towards allergens

Recent approaches to improve AIT have focused on optimizing high allergen-specific IgG titers without activating sensitized allergic effector cells [88]. The properties of allergens can be changed in a way that they become more immunogenic for example by using adjuvants such as aluminium hydroxide (Al(OH)3), microcrystalline tyrosine (MCT), monophosphoryl lipid A (MPLA) and calcium phosphate (CaP)[88]. At the same time, immunization approaches aim to deliver allergens in way that FcεRI cannot be cross-linked on allergic effector cells, causing allergic reactions or anaphylaxis. Examples of strategies to reduce allergen reactogenicity while maintaining immunogenicity include peptide immunotherapy or intra-lymphatic injection [89], [90]. A promising novel platform that combines immunogenicity with a lack of reactogenicity are virus-like particles-based vaccines that are able to induce high protective allergen-specific IgG titers while reducing the allergenicity of the allergen [91], [92]. The immunogenicity of exosomes could be harnessed in similar fashion and could represent a physiological nanoparticle. Hence, exosomes packaged with allergens or p-MHC complexes could be loaded with other components such as co-stimulatory molecules or mRNA/miRNA and modified in a way to target specific cells, a concept that has been proven in mature DCs and MSC [45], [49]. Potentially, the goal of inducing TH1-like immune responses, could even be achieved by just packaging native antigens into exosomes [93]. The ability to induce TH1-like responses using exosome-based vaccines has been reported in multiple studies showing that they can induce IFN-γ, TNF-α T cell responses and boost IgG antibody responses [94]–[96]. In conclusion, a vaccination approach based on exosomes that promotes protective IgG responses which inhibit IgE effector function could be an interesting strategy in allergy immunotherapy (Figure 3).

Figure 3: DC-derived exosomes that boost protective IgG responses

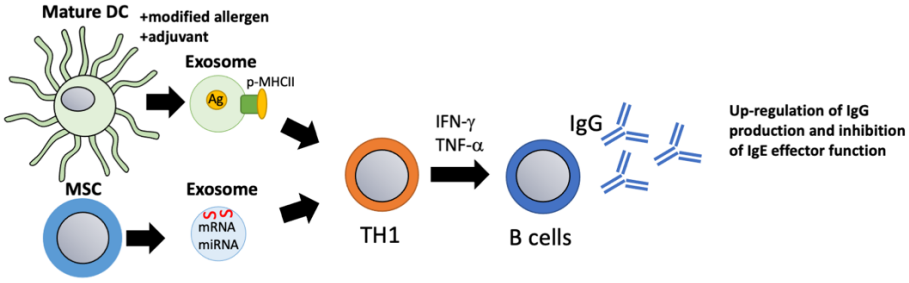

Figure 3: DC-derived exosomes as a vaccination approach that boost protective IgG responses

Exosomes from mature DCs loaded with allergens promote T cell and B cell activation resulting in a classical TH1 type immune response with high IgG titers. This method could be optimized in a number of

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ways for example by addition of specific adjuvants or by packaging allergens that are modified to be more immunogenic.

5.4 Using exosomes to modulate IgE-facilitated antigen presentation

IgE in complex with antigen (Ag) forms IgE-Ag immune complexes that are highly immunogenic and lead to a CD4+ T cell and antibody responses in a process that has been termed IgE-facilitated antigen presentation IgE-FAP [97]–[99]. The mechanism of IgE-FAP involves the low-affinity receptor CD23 expressed in B cells that shuttle IgE-Ag complexes to the follicles where they transfer antigen to dendritic cells [100], [101]. The ligation of CD23 by IgE-Ag immune complexes has functional consequences in allergy in that it negatively regulates IgE levels in the serum in negative feedback fashion by inhibition of IgE responses and down-regulation of serum IgE levels [102]–[107]. There are two CD23 isoforms that differ in their intracellular signaling sequence. CD23a internalizes IgE-Ag complexes via endocytosis whereas CD23b is expressed by a was shown to lead to phagocytic uptake [108]. DCs expressing CD23b degrade antigens while in B cells that mainly express CD23a, the antigen is protected and co-recycled with MHCII to the cell surface [109], [110]. Independently, a study showed that in B cells, CD23-mediated internalization results in ADAM-10 dependent sorting into exosomes [111]. ADAM-10 is the principle sheddase of CD23 and highly expressed in Golgi-derived vesicles, suggesting that CD23 shedding and/or release in exosomes requires endocytosis to allow ADAM10 to bind and to cleave CD23 [112]–[115]. Furthermore, it was shown that in B cells, exosome sorting of CD23 is co-regulated by engagement of the adrenergic receptor β2AR which controls ADAM-10 expression as well as protein expression of CD23 which localize to exosomes [116]. We and others proposed a model in which B cell-expressed CD23 recycles IgE-Ag complexes into exosomes that carry IgE, allergen, MHCII and CD23 which are able to induce T cell proliferation and antibody responses [109], [117], [118]. In conclusion, exosomes derived from CD23-activated B cells could be used to manipulate IgE-facilitated antigen presentation to boost T cell and antibody responses while simultaneously down-regulating serum IgE levels (Figure 4).

Figure 4: B cell-derived exosomes that modulate IgE-Facilitated Antigen Presentation

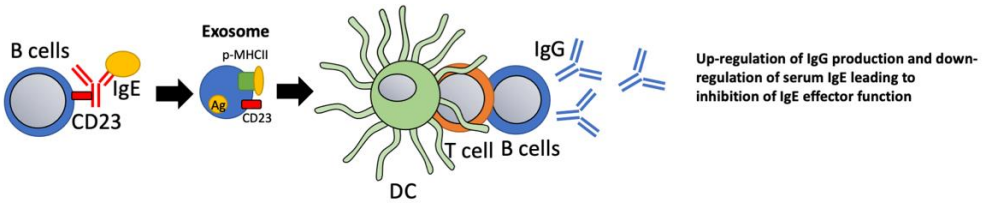

Figure 4: B cell-derived exosomes that modulate IgE-Facilitated Antigen Presentation
B cell mediated sorting of IgE-allergen complexes into exosomes via CD23 could be harnessed to promote protective allergen-specific IgG responses. Targeting CD23 could have the additional effect of down-regulating IgE levels.

8. Conclusion

The general importance of exosomes in the modulation of immune responses as well as their therapeutic value in immunopathology is widely accepted including in allergic diseases which are a major global health burden. AIT, the only disease-modifying therapy for allergic diseases is far from optimized, as it is not available for all allergies, displays strong variations in success rate, requires patients to undergo repeated treatment over long time periods, and often bears risks of side effects. Exosomes driving tolerance or deviating immune responses could represent a future tool for the optimization of allergy immunotherapy. The ability of exosomes to carry p-MHCII complexes and/or native antigens can facilitate strong simultaneous stimulation of T cells and B cells. Additionally, engineering of receptor surface expression such as FcεRIand packaging of mRNA and

miRNA allow endless possibilities in optimizing potential therapeutic candidates. Even though more research in this area is required, we believe that there are multiple intriguing mechanisms by which exosomes could be engineered as therapeutic agents in allergy immunotherapy.

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Conflicts of Interest
The authors declare no conflict of interest

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