



Review article

Bridging micro/nano-platform and airway allergy intervention

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ABSTRACT

Allergic airway diseases, with incidence augmenting visibly as industrial development and environmental degradation, are characterized by sneezing, itching, wheezing, chest tightness, airway obstruction, and hyper-responsiveness. Current medical modalities attempt to combat these symptoms mostly by small molecule chemotherapeutics, such as corticosteroids, antihistamines, etc., via intranasal approach which is one of the most noninvasive, rapid-absorbed, and patient-friendly routes. Nevertheless, inherent defects for irritation to respiratory mucosa, drug inactivation and degradation, and rapid drug dispersal to off-target sites are inevitable. Lately, intratracheal micro/nano therapeutic systems are emerging as innovative alternatives for airway allergy interventions. This overview introduces several potential application directions of mic/nano-platform in the treatment of airway allergic diseases, including carriers, therapeutic agents, and immunomodulators. The improvement of the existing drug therapy of respiratory allergy management by micro/nano-platform is described in detail. The challenges of the micro/nano-platform nasal approach in the treatment of airway allergy are summarized and the development of micro/nano-platform is also prospected. Although still a burgeoning area, micro/nano therapeutic systems are gradually turning to be realistic orientations as crucial future alternative therapeutic options in allergic airway inflammation interventions.

1. Introduction

Respiratory system, which contacts directly with the ever-changing external atmosphere, is a dynamic continuum with large surface area, while confronting a sequence of threats such as outer allergens and pathogens [1]. With the environmental deteriorating and allergenic particulates increasing, allergic airway inflammation such as allergic rhinitis and allergic bronchial asthma with distinctly augmented morbidity, has become one of the most common respiratory system diseases, threatening billions of people including both children and adults worldwide [2–5]. There are a few general strategies for clinical management of airway allergy: avoidance of allergens, rational pharmacotherapy, optional immunotherapy, patient education and follow-up [6–8].

Airway delivery of drugs to improve drug utilization is an attractive route of administration. Nevertheless, current pharmacotherapy of airway delivery reveals certain defects such as irritation to respiratory mucosa via direct contact, relatively uncontrollable drug delivery target site, rapid drug dispersal to off-target sites, etc., and immunotherapy

faces the challenges of inactivation and degradation of antigen proteins or peptides during the delivery process. The barriers of airway delivery, including mucus barrier, mucociliary clearance and enzyme environment, make it difficult for drugs to enter the target site and reduce the accessibility of drugs. The increasing morbidity, far-ranging influence, and accompanied enormous financial and social costs have prompted drastic urgency in illuminating and summarizing novel diagnosis and therapeutical strategies against airway allergy. Micro/nano-platform that can improve drug accessibility, target delivery, and prolong drug residence time has attracted much attention.

Nowadays, large amounts of intratracheal route delivered micro/nano therapeutic systems are emerging, presenting promising potential to overcome the above-mentioned flaws. The design of micro/nano-platform and the properties of carrier materials contribute to promoting the delivery of drugs and allergens. Utilization of intratracheal micro/nano-platform has paved an attractive avenue in the therapy of allergic airway disorders for protecting cargos from being inactivated and degraded, reducing direct irritation to respiratory mucosal, enhancing in situ retention and permeation, and augmenting anti-

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allergic therapeutic efficacy [9–12]. Micro/nano-platform not only can be used as carriers to assist the delivery of other cargos, but also show the potential as therapeutic agents for airway allergy, such as gold nanoparticles, silver nanoparticles and chitosan-based nanoparticles. As therapeutics, micro/nano-platform can act on inflammatory cells and immune cells through a variety of ways to reduce inflammatory response. Immunomodulators composed of antigen and micro/nano-platform greatly improve the immunotherapy for airway allergic diseases. Micro/nano-platform is designed to regulate immune types and induce immune tolerance. Micro/nano-platform has been gradually developed and used in the treatment of airway allergy and we summarize the application of micro/nano-platform and the problems of airway environment and look forward to its future development.

2. Micro/nano-platform for airway allergy management

For the treatment of airway allergy, drug therapy and immunotherapy are the two most important intervention therapies, both of which can be treated through the respiratory tract [13,14]. Given the high compliance of patients with respiratory tract, this is a very potential development direction. The introduction of micro/nano-platform is helpful to the delivery of drugs and allergens in the respiratory tract. As an important auxiliary way, it promotes the development of respiratory tract treatment of airway allergic diseases.

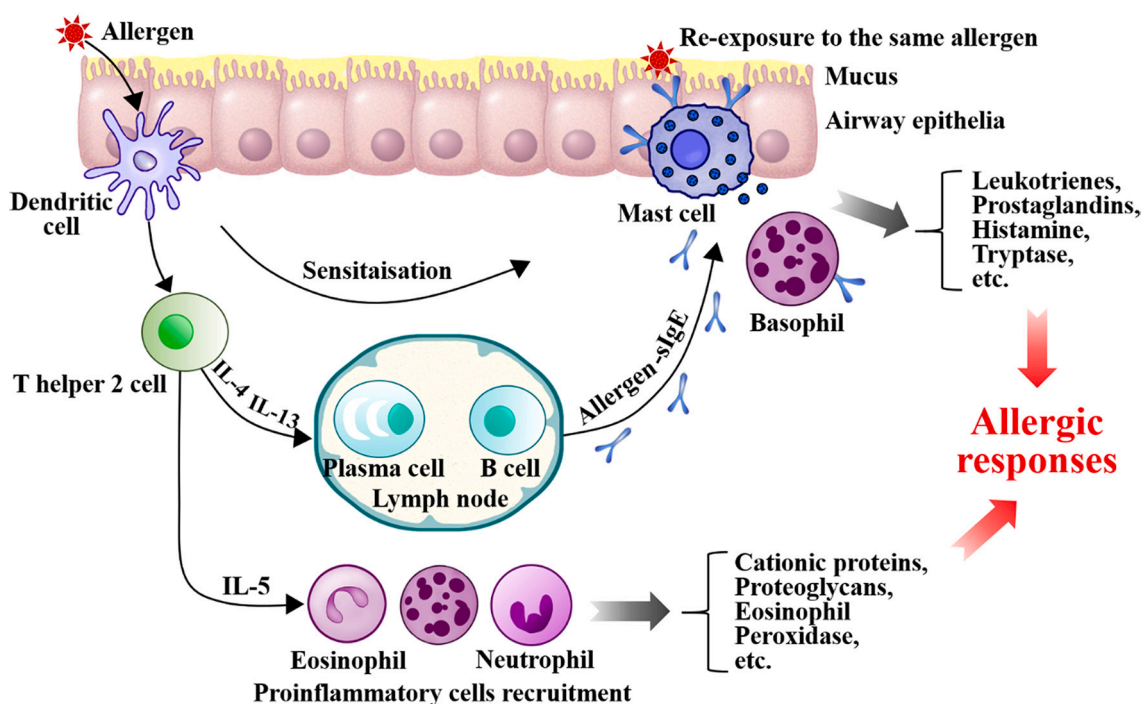
2.1. Pathogenesis of airway allergy

The ruin of the accurate balance state between external environment and internal respiratory tract may lead to a battery of airway diseases including allergic rhinitis, sinusitis, nasal polyps, asthma, etc. [15]. The occurring of allergic airway disorders initiates from close interactions between susceptible mucosal surfaces of airway epithelia with inhaled unstable environmental allergens [16–18]. The pathogenesis of allergic

airway events illustrated in Scheme 1. Once the professional mucosal antigen presenting cells encounter the external allergen or foreign granules in conducting airway, they recognize, process, present the allergen, simultaneously, the conversion of naïve T helper cells to T helper 2 (Th₂) cells occurs by means of mediators and cytokines [19]. Subsequently, a variety of cytokines such as IL-4 and IL-13 are secreted and released by mature Th₂ cells, inducing allergen-specific IgE production by B cells [20]. IgE, in turn, irreversibly binds with the high-affinity receptor (FcεRI) on the cytomembrane surfaces of mast cells and basophils [21], which can prolong their survival time and trigger allergen-specific activation, by then, the cells are in the "sensitized state". Re-exposure of the "sensitized" mast cells and basophils to the same antigen induces its specific coupling with the variable region of IgE bound on the surface of mast cells or basophils, activating the degranulation process of cells from intracellular vesicles [22]. A mass release of preformed mediators and newly synthesized mediators out of mast cells lead to acute early-phase typical inflammatory symptoms, such as sneezing, itching, watery discharge, and airway obstruction [23,24]. Th₂ lymphocytes, eosinophils, basophils, and neutrophils which can secrete a diverse set of pro-inflammatory cytokines and mediators such as eotaxin, superoxide anion, hydrogen peroxide, major basic protein, and eosinophil derived neurotoxin subsequently. The recruitment, adhesion, and infiltration of these cells induce late-phase allergic cascade reactions, characterized by congestion, nasobronchial hyper-reactivity, and airway blockage [25,26].

2.2. Conventional intratracheal therapeutic

Intratracheal delivery route has long been a prospective territory for both topical and systemic delivery as its non-invasive and user-friendly properties, large contact area allowing for rapid drug absorption and permeation, and avoidance of first-pass metabolism of the hepatic system and severe side effects [27,28]. Intratracheal administration can



Scheme 1. Pathophysiology of airway allergy. The contact of inhaled external allergen with DCs at respiratory mucosa triggers the recognition and presenting process, simultaneously, transforms naïve Th cells to Th₂ cells. Cytokines secreted by Th₂ cells induce the overproduction of allergen specific IgE, which binds to the high-affinity receptor on the surface of mast cells and basophils. Re-exposure to the same allergen triggers the degranulation of activated mast cells and basophils, releasing a mass of pro-inflammatory mediators, leading to typical early-phase allergic symptoms, such as sneezing, itching, and watery discharge. Recruitment, adhesion, and infiltration of eosinophils, basophils, and neutrophils and subsequently released a series of pro-inflammatory mediators result in the late-phase allergic responses, such as congestion, nasobronchial hyper-reactivity, and airway blockage.

improve lung selectivity, reduce drug dose and systemic toxicity, and improve patient compliance. According to the known pathogenesis of airway allergy, drug therapy has become an important means of active intervention. Small molecule chemotherapeutants like intranasal corticosteroids, antihistamines, and mast cell stabilizers, etc. aiming either to down-regulate the local release of inflammation-related mediators from activated cells, or to antagonize with the end effector cells membrane receptors against the mediators to suppress severe corresponding symptoms [29–31], are the most widely accepted clinical therapeutic strategies. Furthermore, combined administration of medicines with diverse mode of action has become an orientation, as extensive participation of multifarious inflammatory mediators and effector cells in allergic inflammation, in which single target mediated pharmacotherapy has been proven to be inefficient to relieve all the direct or underlying symptoms [26]. With the understanding of nasal immune mechanism, immunotherapy has become an effective way to improve the quality of life of patients with airway allergic diseases. Immunotherapy is designed to reverse unbalance between Th₁ and Th₂ phenotypes mainly via restraining the release of proinflammatory cytokines and mediators [32], or blocking the binding of secreted IgE with its high affinity receptors on the surface of mast cells and basophils to achieve desensitization of effector cells [22,33–35]. General paths of immune strategy are to administrate allergen extracts, recombinant allergens, chemically altered allergens, cell epitope peptides, etc. with gradually increasing doses via subcutaneous, intraepithelial, oral, nasal, or bronchial routes to establish immune tolerance [36,37].

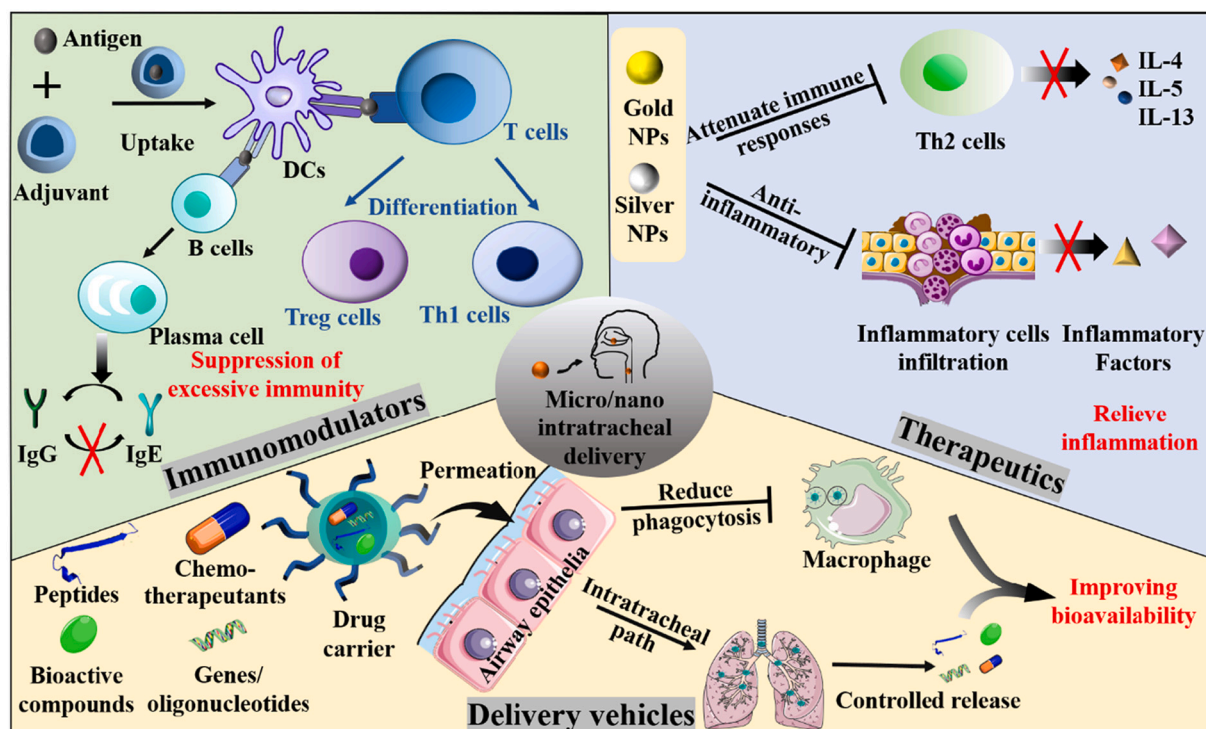
2.3. Improve airway allergy therapy through micro/nano-platform

Intratracheal therapeutic is undoubtedly a way of administration with high compliance and accessibility [38]. However, it is difficult to deliver drugs or allergens through the epithelial of respiratory tract. The clearance mechanism of nasal epithelium and mucosal barrier make it

difficult for drugs and allergens to enter the therapeutic target effectively. Mucociliary clearance mechanism in the nasal hinders the penetration of drugs into the mucus layer and diffusion to the lungs [39]. The co-delivery of micro/nano-platform and drugs can realize the colocalization of multiple drugs and enhance the retention time of drugs in nasal cavity and mucosal permeability [40]. For drugs with poor solubility, intranasal delivery is facing more difficulties. Suspension formed by micro nano system can improve solubility and expand the types of nasal delivery drugs [41]. Another advantage of the micro/nano-platform is that it can protect the drug molecules from degradation in the nasal environment, and realize the targeted release of drug molecules [42]. Although there are only a few types with therapeutic effects at present, the introduction of anti-inflammatory micro/nano-platform into the treatment of airway allergy can improve the therapeutic effect. It can be used as an immunomodulator to promote the induction of immune tolerance. These advantages indicate the potential of the micro/nano-platform in respiratory drug delivery (Scheme 2). Furthermore, the micro/nano-platform can be delicately designed to reach and deposit in specific airway areas, achieve homogeneous distribution, and provide multiple therapeutic modes, by tailoring the particles diameters, hydrophilic/hydrophobic balance, or other surface properties [43–45], which need much focus. We also highlight the recent paradigms of airway allergy (mainly allergic rhinitis and allergic asthma) managements utilizing micro/nano-platform and offer our perspectives on the plausible advances in the related field by and by.

3. Micro/nano-platform as delivery vehicles

In the domain of airway allergy interventions, micro/nano-platform manufactured as delivery vehicles take up the most extensive status, carrying varieties of cargos such as chemotherapeutants, peptides, genes/oligonucleotides, and bioactive compounds, which are listed in Table 1.



Scheme 2. Application of micro/nano-platform in the treatment of airway allergy. As delivery vehicles, micro/nano-platform can improve the delivery effect of drugs via intratracheal path, facilitate drug penetration through the epithelial barrier, reduce macrophage phagocytosis and achieve sustained drug release. Micro/nano-platform as therapeutics can inhibit the activity of airway allergy related inflammatory cells by regulating the production of reactive oxygen species, inhibit secretion of Th₂ cytokine. As immunomodulators, micro/nano-platform can effectively enhance the uptake and activation of DCs, promote the transformation of plasma cell type and inhibit Th₂ immune response by activating Treg cells and Th₁ cells.

Table 1

Micro/nano-platform as delivery vehicles in airway allergy interventions.

Payloads	Micro/nano-platform	Characteristics	Type of study	Administration route	Targeted diseases	Ref
Chemotherapeutants	Chitosan swellable microparticles	1. Particle sizes of 3.2–3.7 μm ; 2. ~80% release of loaded-budesonide within 12 h; 3. Sustained curative effect under half dose and long interval.	<i>In vivo</i> (BALB/c mice and Sprague Dawley rats)	Intratracheal inhalation	Allergic asthma	[46]
	Porous poly (lactide-co-glycolide)-poly (vinyl pyrrolidone) microparticles	1. Particle sizes of 9.2–20.1 μm ; 2. ~90% release of loaded-budesonide within 72 h; 3. Decreased macrophages uptake; 4. Increased lung residue.	<i>In vitro</i> (RAW264.7 macrophages) and <i>in vivo</i> (Sprague Dawley rats)	Intratracheal inhalation	Allergic asthma	[47]
	Starch- α -, β -, or γ -cyclodextrin microspheres	1. Particle sizes of 50–160 μm ; 2. ~100% release of loaded-Gabexate Mesylate within 1 h; 3. Bio-adhesion to nasal mucosa.	/	Intranasal route	Allergic rhinitis	[48]
	Hydroxypropyl- β -cyclodextrin microparticles	1. “Deflated-ball like shape” particles with sizes of 3.11 μm ; 2. Decreased budesonide permeability out of lung.	<i>In vitro</i> (Calu-3 bronchial epithelial cells) and <i>in vivo</i> (BALB/c mice)	Intranasal instillation	Allergic asthma	[49]
	Fluorescent dye DY-647 hybrid nanoparticles	1. Particle sizes of 31 nm; 2. Higher anti-inflammatory effect than free betamethasone phosphate; 3. Up-taken by alveolar M2 macrophages; 4. <i>In vivo</i> optical imaging and real-time monitoring.	<i>In vitro</i> (MH-S macrophages) and <i>in vivo</i> (BALB/c mice)	Intranasal instillation	Allergic airway inflammation	[50]
Peptides	Vanillyl alcohol-containing copolyoxalate (PVAX) microparticles	1. Particle sizes of 13 μm ; 2. ~90% release of loaded-dexamethasone (DEX) within 25 h; 3. Unique antioxidant activity; 4. Synergistic curative effect of PVAX microparticles and DEX.	<i>In vitro</i> (RAW 264.7 (macrophages and L2 pulmonary epithelial cells) and <i>in vivo</i> (BALB/c mice)	Intratracheal injection	Allergic asthma	[51]
	α -alumina nanoparticle	1. Particle sizes of 85 nm; 2. Effective protection of loaded vasoactive intestinal peptide (VIP) from enzymatic degradation; 3. Better curative effect than VIP alone.	<i>In vivo</i> (BALB/c mice)	Intratracheal inhalation	Allergic asthma	[52]
	Plasmid DNA and block copolymers of poly-L-lysine and polyethylene glycol nanoparticles	1. Flexible rod-like particles with sizes of 89 nm; 2. Mediating airway gene transfer and improving lung retention; 3. Satisfactory curative effect after a single dosing.	<i>In vivo</i> (BALB/c mice)	Intratracheal route	Allergic asthma	[53]
Genes/oligonucleotides	Chitosan-oligodeoxynucleotide nanocomplexes	1. Particle sizes of 189–278 nm; 2. Improved physicochemical stability; 3. Improved <i>in vitro</i> transfection efficiency of IL-5 antisense oligodeoxynucleotide.	<i>In vitro</i> (H1299 epithelial cells and D10. G4.1 murine Th ₂ cells) and <i>in vivo</i> (BALB/c mice)	Intranasal route	Allergic rhinitis	[54]
Bioactive compounds	Poly (ethylene glycol)-block-poly (D, L-lactide) micelles	1. Particle sizes of ~18 nm; 2. ~80% release of loaded-xanthatin within 30 h; 3. Effective promoting immune tolerance by upregulating Treg cells level.	<i>In vitro</i> (bone-marrow derived DCs) and <i>in vivo</i> (C57BL/6J mice)	Intranasal route	Allergic rhinitis	[55]

3.1. Chemotherapeutants delivery

The currently available intranasal small molecule chemotherapeutants such as glucocorticoids, antihistamines, mast cell membrane stabilizer, etc., face the flaws of high *in situ* initial drug concentration followed by inexpectant side effects and rapid drug dispersal to off-target sites [56], short retention and acting time requiring frequent dosing [46,47], leading to irritation to respiratory mucosa [57], etc., which can be obviated with controlled and sustained delivery and release systems, for example, micro/nano delivery vehicles.

3.1.1. Chitosan-based micro/nano-platform

Chitosan, a linear semi-crystalline biopolymer, is a vital promising micro/nano-platform fabricated material for chemotherapeutants delivery, given its splendid properties of abundant availability, intrinsic biodegradability, tissue compatibility, high charge density, and tunable biological characters [58–60]. The cationic character confers chitosan with mucoadhesive property and ability to enhance drugs permeation and absorption through mucosa such as the nasal, intestinal, ocular, or pulmonary barriers [61], which is crucial for vehicles to achieve effective airway delivery. When delivering via respiratory tract, chitosan-based micro/nano-platform would bind with the negatively charged sialic acid residues of membrane bound glycoproteins on mucosal

surfaces by means of electrostatic adsorption [62], thus exhibiting longer *in situ* retention, and delayed phagocytosis of alveolar macrophages, allowing adequately release of the curative payloads [63].

Several studies have elucidated the potential of chitosan-centered micro/nano-platform in allergic airway inflammation intervention via intratracheal route. Nasal cavity environment adaptive deoxycholate/cetirizine-chitosan-hydroxybutyl nanoparticles (CDHBCs-NPs) were generated aiming to successfully encapsulate and deliver antihistaminic therapeutic cetirizine [57]. The CDHBCs-NPs prolonged the total chemotherapeutant release time via a two-step mode (pH-responsive drug leakage and lysozyme-mediated sustained releasing), which hold tremendous potential as nasal cavity targeted delivery vehicles in allergic rhinitis intervention. Hydroxybutyl chitosan coated ketotifen and cetirizine for the treatment of allergic rhinitis achieved long-term drug release, reduced the dosage, and improved the therapeutic effect (Fig. 1B) [64]. Budesonide-loaded chitosan swellable microparticles were engineered to achieve delicate pulmonary anti-allergy drug delivery, and meanwhile, the correlation of *in vitro* drug release with *in vivo* efficacy was established (Fig. 1A) [46]. Administrated to allergic asthma model, budesonide-chitosan microparticles displayed effective drug delivery towards deep lungs, and the swellable microparticles sustained the budesonide release time and prolonged the anti-allergic therapeutic effect even at reduced dosing frequency (once every 2

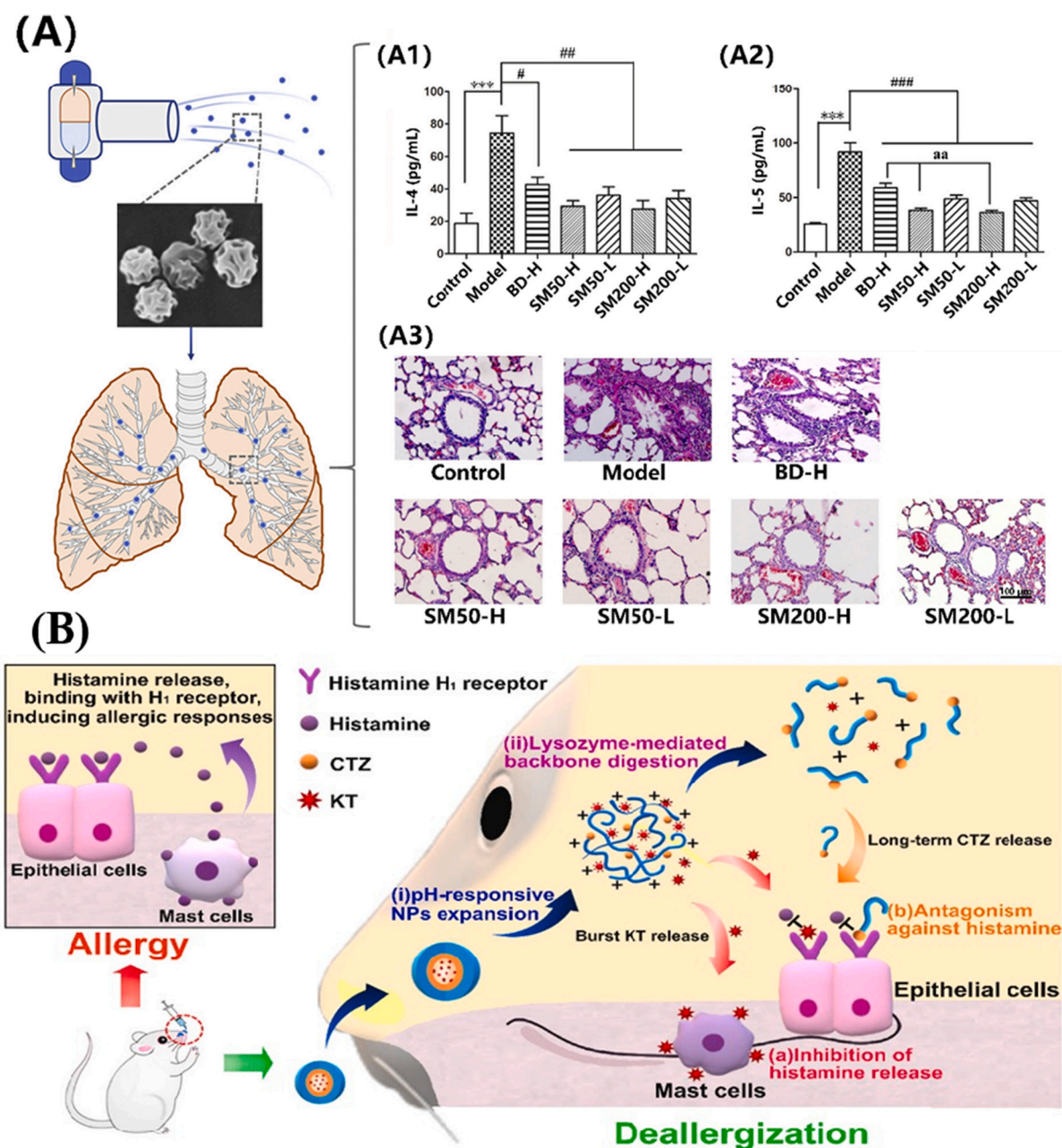


Fig. 1. (A) Budesonide-incorporated chitosan swellable microparticles are correlated with improved pathophysiology. IL-4 (A1), IL-5 (A2) levels in BALF, and representative lung slices (A3) after pulmonary delivery of budesonide physical mixture with high dose (BD-H), chitosan (molecular weight of 50 kDa) swellable microparticles with high dose (SM50-H) and half dose (SM50-L), chitosan (molecular weight of 200 kDa) swellable microparticles with high dose (SM200-H) and half dose (SM200-L). (B) Diagram of KT coated with CTZ modified hydroxybutyl chitosan nanoparticles. The response to pH (5.5) in nasal cavity led to burst release of embedded ketotifen, while hydrolysis mediated by lysozyme resulted in long-time release of grafted cetirizine, achieving not only rapid relieving of symptoms but also sustained anti-allergic curative effect. Reproduced with permissions from [46,64]. Copyright 2018 Elsevier, 2021 Elsevier.

days) as well as decreased drug dose (half dose), which may find extensive application in local lung diseases therapy.

3.1.2. Poly (lactide-co-glycolide)-based micro/nano-platform

Poly (lactide-co-glycolide) (PLGA), a synthesized polymer composed of glycolic acid and lactic acid units [65], has paved the path in the domain of pharmaceutical and biomedical sciences. Nowadays, it has gained thriving attention to structure micro/nano-scaled systems for specifically targeted and controlled delivery of multiple micro and macromolecules, attributing to its splendid features such as biocompatibility and biodegradability, practicable surface modifications, feasibility to attain sustained payload release, and well-described

synthesis approaches [66–68]. Being approved by FDA for drug delivery [69], PLGA-based micro/nano-platform has utilized as intratracheal vehicles for allergic airway inflammation management. Inhalable porous PLGA particles incorporated with budesonide were generated as lung delivered formulations and the *in vitro/in vivo* correlation was established to measure the *in vivo* performance (e.g., systemic exposure and curative efficacy) via *in vitro* drug release behavior [47]. Porous particles with various diameters and pore sizes presented approximate 75% reduction of RAW264.7 macrophages uptake compared with budesonide/lactose physical mixture. Moreover, the formulations were proven to enhance the payload retention in lungs of rats and to accelerate allergic inflammation elimination, verifying to be more effective

strategy over physical mixed formulations.

3.1.3. Cyclodextrin-based micro/nano-platform

Cyclodextrins, a class of cyclic oligosaccharides, are generally employed in biomedical and pharmaceutical fields, attributing to its convenient availability, rigid and well-defined structures, water-solubility, and nontoxicity [70]. Moreover, their capability to form sophisticated supramolecular structures using simple organic/inorganic/biological molecules and ions [71], confers them considerable potential as promising building blocks to construct functional nano-scaled

architectures [72]. Recently, cyclodextrin-based micro/nano-platform as intratracheal vehicles to deliver chemotherapeutics have been proposed. For instance, bioadhesive starch/ α -, β -, or γ -cyclodextrin microspheres embedded with antiallergic Foys were established to form stable allergic rhinitis therapy complexes [48]. Although the microspheres presented relatively rapid Foys cargos release behaviors (within 1 h), such particles were treated as potential nasal administration platforms for allergy management since the sufficient adhesion of drug loaded microspheres to nasal mucosa distinctly prolonged the retention time over free Foys alone. Moreover, hydroxypropyl- β -cyclodextrin was

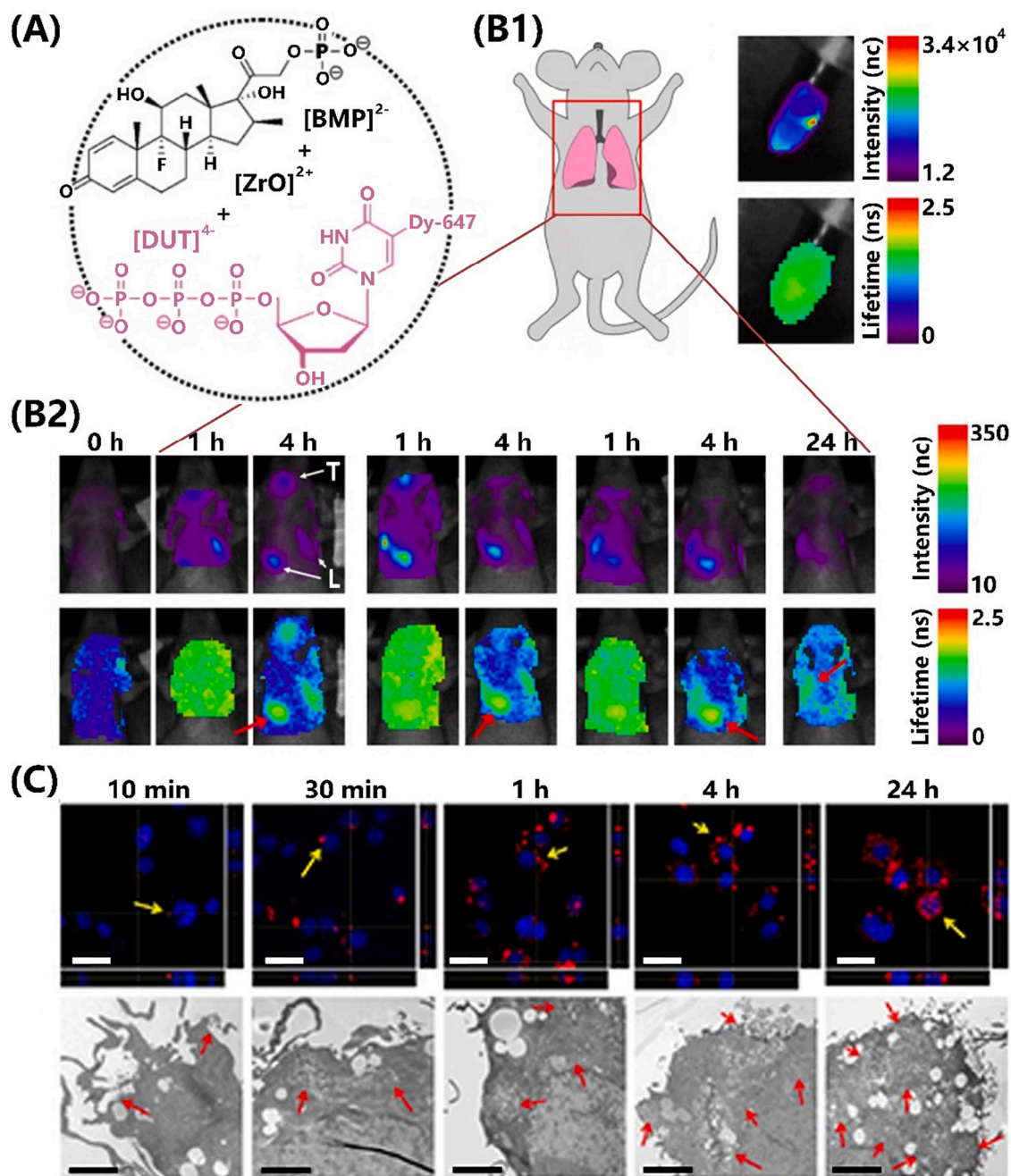


Fig. 2. (A) Chemical composition of BMP-DY-647 hybrid nanoparticles (BMP-IOH-NPs); (B) Biodistribution of BMP-IOH-NPs in mice model with allergic airway inflammation monitored by real-time epi-fluorescence imaging. (B1) Scan of BMP-IOH-NPs stock solution presenting fluorescent intensity (upper panel) and lifetime (lower panel), and (B2) *in vivo* accumulation of BMP-IOH-NPs post intranasal instillation. High density fluorescence was detected in pharynx/trachea (T) and lung (L) after 1 h post instillation, and subsequently, fluorescence merely remained in lung and finally disappeared after 24 h. (C) Uptake of BMP-IOH-NPs by alveolar MH-S macrophages via confocal fluorescence microscopy (red: BMP-IOH-NPs, blue: DAPI) and electron microscopy. Cellular internalization was detected after 10 mins' co-incubation and continuously increased over time (arrows). The NPs were localized within vesicle of MH-S macrophages, implying the cells acted as reservoir for sustained BMP releasing. Reproduced with permission from [50]. Copyright 2018 Ivyspring.

utilized to assemble dried inhalable microparticles formulation which could release therapeutic budesonide payloads continuously in lung fluid [49]. Microparticles in the form of specific “deflated-ball like shape” with diameters of 3.11 μm which was appropriate for inhalation, exhibited superior abilities to aerosolize active ingredients and further dissolve in lung fluid, aiming to decrease permeation out of lung to obtain optimized profiles. The inhalable cyclodextrin-budesonide microparticles attested higher anti-inflammatory effect over simple budesonide formulations in mouse model of asthma, therefore was of particularly interest to improve lung-targeted delivery while decreasing high dose of budesonide mediated systemic side effects.

3.1.4. Other micro/nano-platform for chemotherapeutant delivery

These years, diversified micro/nano-platform with more complicated and accurate fabrication for chemotherapeutants delivery are emerging to combat airway allergic symptoms. Novel navigational platform of therapeutic chemotherapeutant-encapsulated fluorescent hybrid nanoparticles consisting of glucocorticoids BMP and fluorescent dye molecules (BMP-IOH-NPs) was reported to improve the anti-allergic curative effect with simultaneous *in vivo* imaging (Fig. 2) [50]. *In vitro* MH-S macrophages uptake of BMP-IOH-NPs was observed during the first 10 mins' incubation, and the anti-inflammatory effect of BMP-IOH-NPs was dose-dependent and higher than that of the gold standard dexamethasone (DEX) and free BMP, confirming efficient release of the cargos out of NPs and cells. *In vivo* accumulation of BMP-IOH-NPs within the lungs in allergic airway inflammation mice was preferentially detected in peribronchial and alveolar M2 macrophages via real-time imaging 4 h after intranasal administration. Treated with BMP-IOH-NPs, eosinophil numbers in BALs of model mice decreased significantly, with immune cell infiltration in lungs reduced, revealing the validity of BMP-IOH-NPs in airway allergy therapy and simultaneous fluorescence tracking potential.

Copolyoxalate, biodegradable and biocompatible, has recently been utilized for biomedical applications as suture coating and delivery vehicles [73]. For instance, vanillyl alcohol-containing copolyoxalate was constructed as a novel polymeric prodrug, in which vanillyl alcohol (scavenging hydrogen peroxide to exert potent anti-oxidant and anti-inflammatory activity) was covalently grafted onto the copolyoxalate skeleton via hydrogen peroxide-responsive peroxalate ester bonds [51]. Porous microparticles alone reduced oxidative stress and suppressed expression of pro-inflammatory tumor necrosis factor- α (TNF- α) and inducible nitric oxide synthase (iNOS) in activated mouse macrophage (RAW264.7) cells and allergic asthmatic lung of mice. Moreover, steroidal anti-allergic drug DEX co-formulated microparticles exhibited significantly meliorative curative effects than microparticles alone, implying the synergistic effects of DEX in allergic airway inflammatory diseases especially allergic asthma therapy.

3.2. Peptides delivery

Since multiple active peptides in a wide variety of biomedical applications are appearing [74,75], micro/nano-platform for therapeutic peptides delivery have been proposed in allergic airway inflammation interventions. For instance, Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) has been proven to stimulate the generation of reactive oxygen species (ROS) [76,77], and played a pivotal role in forming allergic asthma phenotypes [78,79]. Towards this, CaMKII inhibitor peptide (Camikini) incorporated PLGA nanoparticles were fabricated and coated with cationic chitosan for effective and targeted pulmonary delivery [80]. CaMKII-PLGA NPs down-regulated the severity of allergic asthma in murine model by reducing key disease phenotypes, and the modification of chitosan coating increased the total cell uptake in lung, leading to obvious reduction of typical symptoms including mucus production and airway hyperreactivity. As such, bioactive CaMKII peptide delivery provided an efficacious rationale as a promising anti-allergic option against asthma.

In the domain of allergic inflammation interventions, recently emerged vasoactive intestinal peptide (VIP), a 28-amino acid neuropeptide isolated from gastrointestinal tract [81], displays potency as promising airway smooth muscle cell relaxant [82,83], as well as immunomodulatory and anti-inflammatory agent [84–86]. Recently, curative effect of VIP-embedded α -alumina nanoparticles (α -AN) was investigated [52], in view of the superior characters of functional nano-scaled metallic oxides, especially ternary metal oxides, for their high mechanical strength, refractoriness, corrosion resistance [87,88], benign cargo loading capability, ease to fabrication [89–93], and adjustable biochemical properties via suitable surface coating [94–96]. The VIP-embedded α -AN composites were of ~ 80 nm, with 38% of the conjugated peptide releasing post 10 h-incubation in bronchoalveolar lavage (BAL, pH = 6.5). Enzymatic degradation and potency loss of VIP in respiratory tract was avoided to some extent in the form of conjugated composite, and α -AN-VIP conjugation was verified to be more effective in reversing degree of allergic asthma over single component (beclomethasone or VIP) alone ($P < 0.05$).

3.3. Genes/oligonucleotides delivery

Nowadays, curative genes or oligonucleotides delivery via polymer-based micro/nano-platform have been partially put forward by several groups in allergic airway inflammation interventions. Specifically, in view of the excessive augmented Th_2 cytokines level in the development of allergic inflammation, such as IL-5, resulting in eosinophil overproduction, homing and survival, and overexpression of membrane receptors and mediators [97–99], efforts targeted IL-5 have been proposed recently. Nano-sized condensation complexes (named as chitoplexes) were generated consisting of IL-5 antisense oligodeoxynucleotide (AS-ODN) and water-soluble chitosan (40 kDa) for allergic inflammation interventions [54], as chitosan was proven to possess considerable potential to avoid oligodeoxynucleotides degradation and enhance transfection efficiency [100–106]. Compared to naked IL-5 AS-ODN, the chitoplexes enhanced the *in vitro* transfection efficiency into H1299 epithelial cells, and decreased the extracellular IL-5 content in D10.G4.1 murine Th_2 cells. In the allergic rhinitis murine model, condensed chitoplexes were verified to regulate the IL-5 secretion and IgE titer, exhibiting considerable potentiality in the treatment of IL-5-related allergic disorders.

Moreover, lipid carriers especially cationic liposomes have also been investigated as non-viral delivery vehicles for antisense oligonucleotide delivery in allergy managements [107], owing to biosafety, large packaging capacity, ease of chemical modification [108], as well as their ability to bind with negative charged cell membranes, thus inducing the absorptive endocytosis [109–112]. Specifically, pegylated cationic liposomes incorporated with antisense oligonucleotide complementary to mmu-miR-145a-5p (named as anti-miR-145) which aiming to regulate epithelial-mesenchymal transitions were exquisitely constructed to circumvent mucus barriers and combat drug resistance in house dust mite-induced asthma mouse model [113]. Lipid-anti-miR-145 nanocomposites which distributed most in lung parenchyma cells of lower airways reduced the upregulated asthma-related genes levels, reversed eosinophilia, mucosal metaplasia, immunoreactivity, and prevented obstructive airway remodeling, establishing promising pulmonary oligonucleotides delivery option. Besides oligonucleotides, gene delivery via polymeric nano-vehicles has also been proposed in the management of allergic airway inflammation [53], presenting satisfactory inflammatory modulation ability. The toxicity of cationic liposomes is mainly associated with cationic properties and hydrophobic groups. The interaction of positively charged primary amine, secondary amine, tertiary amine, or quaternary ammonium salt in cationic liposomes with critical enzymes such as protein kinase C causes cytotoxicity [114]. Cationic liposomes with low toxicity were successfully developed by delocalizing the positive charge into a heterocyclic ring or neutralizing the positive charge. The toxicity of liposome hydrophobic chain may be related to its

inhibition of protein kinase C. Although the effect of hydrophobic chain on toxicity is not completely clear, low toxic hydrophobic groups are designed to reduce the toxicity of cationic lipid carriers [115,116].

More recently, multiple bioactive compounds against allergic diseases are emerging and have opened new orientations in airway allergy interventions. For instance, increased bilirubin (final metabolite of heme catabolic pathway) content in serum was proven to transiently alleviate allergic asthma symptoms [117], and based on the finding,

"unconjugated" bilirubin was subsequently verified to moderate vascular cell adhesion molecule-1 (VCAM-1)-related airway inflammation [118]. Bilirubin-nano-platform composites presented satisfactory immunomodulatory and therapeutic effect against allergic disorders [119]. Moreover, anti-allergic curative effects of bioactive compounds extracted from traditional folk herbs have been extensively explored in airway allergy interventions [120,121]. Recently, DCs specifically targeted cyclic peptide moiety (NGR)-centered copolymeric micelles (PM) were

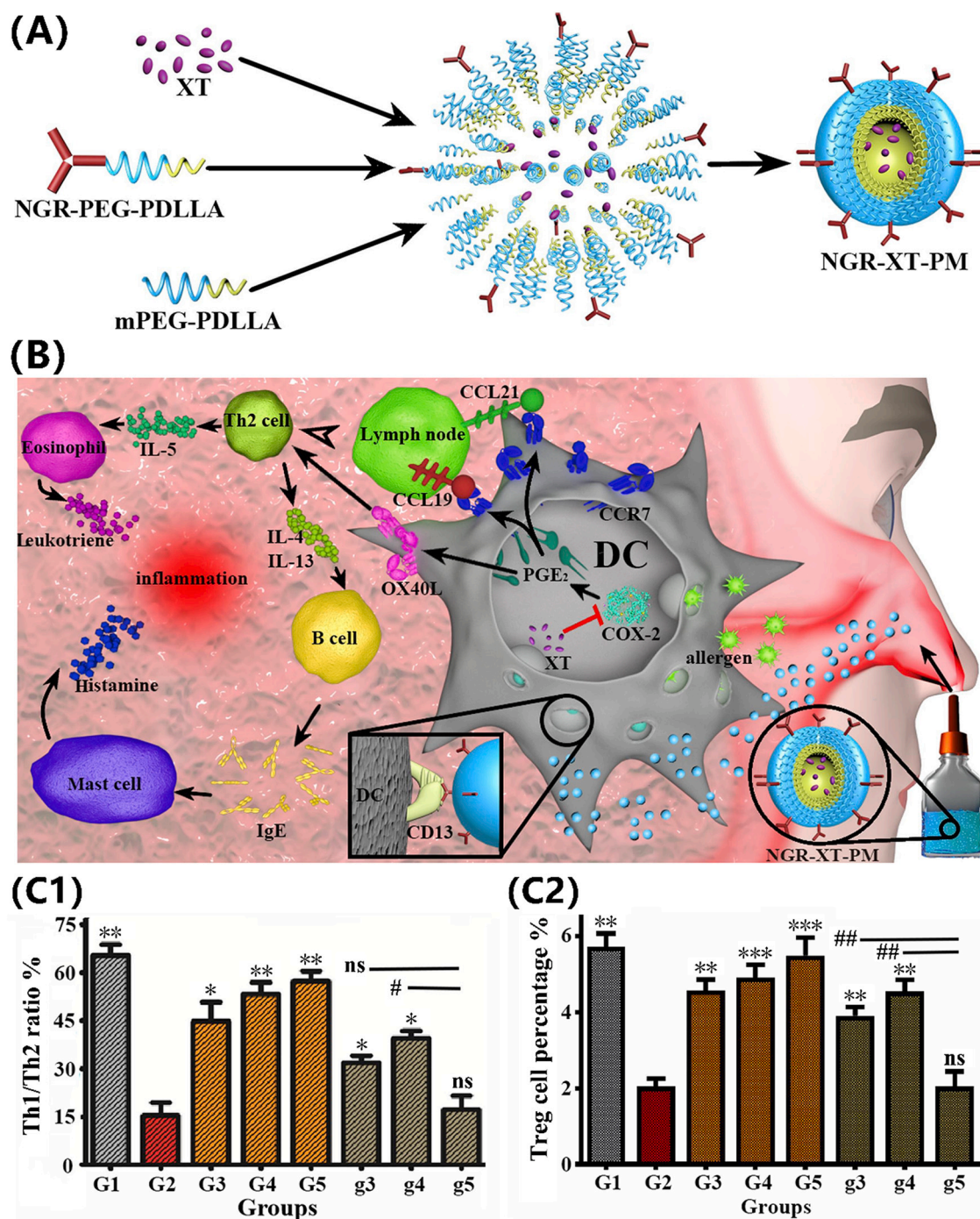


Fig. 3. (A) Schematic diagram of DCs targeted cyclic peptide moiety (NGR)-centered polymeric micelle (PM) incorporated with therapeutic *Xanthatin* (XT), named as NGR-Xt-PM. (B) Graphic anti-allergic mechanism of NGR-Xt-PM. Th1/Th2 ratio (C1) and numbers of Treg cells (C2) in mice spleen after intranasal administration of (G1: Normal group; G2: allergic rhinitis group; G3: XT-PM group; G4: NGR-Xt-PM group; G5: Budesonide group; g3: XT-PM relapse group; g4: NGR-Xt-PM relapse group; and g5: Budesonide relapse group). NGR-Xt-PM was targeted to DCs via NGR-mediated endocytosis. The released XT was able to down-regulate the COX-2/PGE2 pathway, thereby obstructing two key downstream signal pathways, and finally reversing excessive differentiation of Th2 cells and relieving allergic responses. Reproduced with permission from [55]. Copyright 2020 Elsevier.

constructed and conjugated with *Xanthatin* (XT) (NGR-XT-PM), a bioactive constituent isolated from *Xanthium strumarium* L. which was proven to render maturation-resistant of DCs for refractory allergic rhinitis therapy [55]. The validity of NGR-XT-PM to effectively reverse Th₁/Th₂ unbalance was verified by down-regulating serum inflammatory factors levels (IgE, histamine and IL-4) and surface costimulatory molecules of DCs (CD80, CD86 and I-A/I-E), meanwhile, immune tolerance was established by up-regulating the recruitment of Treg cells and blocking COX-2/PGE2 signaling pathway. The *in vivo* immunosuppressive and anti-inflammatory efficiency of XT conjugates did not relapse, by contrast with the recrudescence of commercial budesonide treated allergic rhinitis mice, providing optional DCs specifically targeting strategy to restrain refractory allergic response (Fig. 3). Such effective paradigms further motivate the enthusiasm to exploit novel anti-allergic bioactive compounds and broaden the delivery options for airway allergy managements.

3.4. Immunogenicity of delivery system

As a delivery system of allergic drugs, the immunogenicity of micro/nano-platform has an important impact on the therapeutic effect. Chitosan is often used as an immune adjuvant to enhance the immunogenicity of vaccines and has a specific inducing effect on Th₁ immune response, the immunogenicity of chitosan contributes to the treatment of airway allergy by reducing T₂ response [122,123]. As a common polymer micro/nano-platform material, PLGA can promote the maturation of DC. The immunogenicity test of PLGA micro/nano-platform showed that it was safe as a drug delivery system and enhanced the anti-inflammatory effect of airway allergic drugs without toxicity [124,125]. Cyclodextrins with the effect of reducing immunogenicity are used as delivery carriers in combination with other materials [126]. The immunogenicity of liposome delivery system is related to its platform size, charge, and other properties [127]. In the treatment of sensitized animal models, the delivery system does not show obvious immunogenicity, but significantly improves the therapeutic effect of drugs.

4. Micro/nano-platform as therapeutics

With the development of micro/nano-platform, many new properties have been found. In the field of airway allergy treatment, micro/nano-platform show therapeutic effect, which can alleviate the symptoms of airway allergy. This kind of micro/nano-platform provides a new treatment idea in the treatment of airway allergy to enhance the therapeutic effect.

4.1. Gold nano-platform

In current scenario, the in-depth exploration of advanced materials in medical domain is progressively augmenting, in consideration of the budding expansion of nano-structured materials in imaging, diagnosis and therapeutics [128,129]. Nano-scaled noble metal particles such as platinum, gold, and silver, to construct functional precursors or therapeutic agents, have been recently regarded as indispensable materials for innovative nano-platform design [130–134]. The unique characteristic of nano-gold initiates broadening bio-medicinal applications such as magnetic resonance and X-ray computed tomography imaging [135], photo-thermal nanotherapy against tumor [136], biomolecules delivery [137], as well as potential anti-inflammatory and anti-allergic utilities [138]. Recently, well-dispersed and pure gold nanoparticles (GNP) with face-centered cubic lattice crystals were biosynthesized using *Caffeoyl-xanthiazonoside* (CFX), isolated from *Xanthium strumarium* L. fruits as anti-allergic agents [139]. The GNP with diameters of 5–30 nm were proven to inhibit nasal mucosa hyperplasia, ameliorate inflammatory cells infiltration, and down-regulate the overproduction of Th₂ cytokines (Fig. 4A, B). Likewise, extrapulmonary organs distribution of 9-nm

citrate/tannic-acid-coated (citratd) and 6-nm polyethylene-glycol-coated (PEGylated) GNP via airway delivery were detected in BALB/c-mice with asthma-like airway inflammation, and their anti-asthma therapeutic potential were also investigated [140]. Systemic uptake of PEGylated nano-gold was higher than that of citrated nano-gold after respiratory application, especially in spleen, since different agglomeration kinetics of citrated and PEGylated nano-gold appeared (citrated GNP agglomerated rapidly in physiological fluids, while PEGylated GNP remained relatively stable) (Fig. 4C, D). Nano-gold was verified to inhibit both allergy-related immune cells infiltration and airway hyperreactivity, especially the citrated modified ones. Though nano-gold might be of therapeutic benefit, explicit anti-inflammatory pharmacokinetics, detailed anti-allergic mechanism of action, systemic adverse effects, and metabolic kinetics which has rarely been illustrated in the presented work, are eager to be explored and illustrated.

4.2. Silver nano-platform

As mentioned above, noble metal NPs have attracted increasing focus due to their usable applications in a diverse range of subject areas, involving catalysis, nano-scaled electronics, and diseases intervention [141–143]. Nano silver, as one of the most popular noble metal NPs candidate, presents remarkably unusual physicochemical characteristics, such as potent anti-microbial, anti-inflammatory, pro-healing properties [144–148], as well as potential anti-allergic utility. Capsulated nano-silver colloid with ~1.5-nm mean diameter was verified to relieve nasal phlogosis and airway hyperresponsiveness in model mice with allergic airway diseases [149]. Th₂ cytokines, inflammatory cells infiltration, goblet cell hyperplasia, and oxidative stress, determinant of allergic disorders were visibly attenuated after utility of nano-scaled silver.

The potential anti-allergic molecular mechanism has recently been expounded that nano silver is able to attenuate Th₂ oriented immune responses via regulating ROS generation, including oxygen free radicals and other oxygen-containing molecules [150]. Overproduced ROS from eosinophils, alveolar macrophages, and neutrophils, appears to induce airway smooth muscle contraction, impairment of β -adrenergic receptors, influx of inflammatory cells, mucus over-secretion, and high vascular permeability [151], resulting in activation of nuclear NF- κ B, multiprotein complex which is known to activate early immune and inflammation associated genes [152,153]. In OVA-challenged asthma mice, nano silver was verified to relieve excessive oxidative pressure, furthermore down-regulate NF- κ B expression, thus reducing the inflammatory cells recruitment, infiltration and activation, airway hyperresponsiveness, and IL-4, IL-5, and IL-13 levels [150]. Though presenting favorable anti-allergic validity, controversy such as vague pharmacokinetics and toxicology [154], location of ROS scavenging, optimal nano-silver concentrations, and diameters, remains [155], which need to be urgently explored.

5. Micro/nano-platform as immunomodulators

Potential immunomodulatory effect of antigen-modified micro/nano-platform are recently been emphasized, especially OVA-related micro/nano-platform, which are designed to induce the production of regulatory T (Treg) cells and protective IgG antibodies to further block the IgE-mediated end effector cells activation [156,157]. Moreover, antigen-modified spherical nano-platform are proven to arouse strong humoral immune responses, and small scaled nanoparticles (< 100 nm) which are inclined to penetrate tissue barriers and traffic to the draining lymph nodes, can induce more robust immune responses [158,159]. The over-enhanced IgE and IgG1 titers after administration of OVA nanoparticles (OVA NPs) than of OVA were reported by Lv and co-workers [160]. Surprisingly, OVA-specific IgE, OVA-specific IgG1, CD4⁺ T cells and memory B cells declined significantly in animal model treated with curcumin (CUR)-incorporated OVA NPs than CUR alone. OVA NPs were

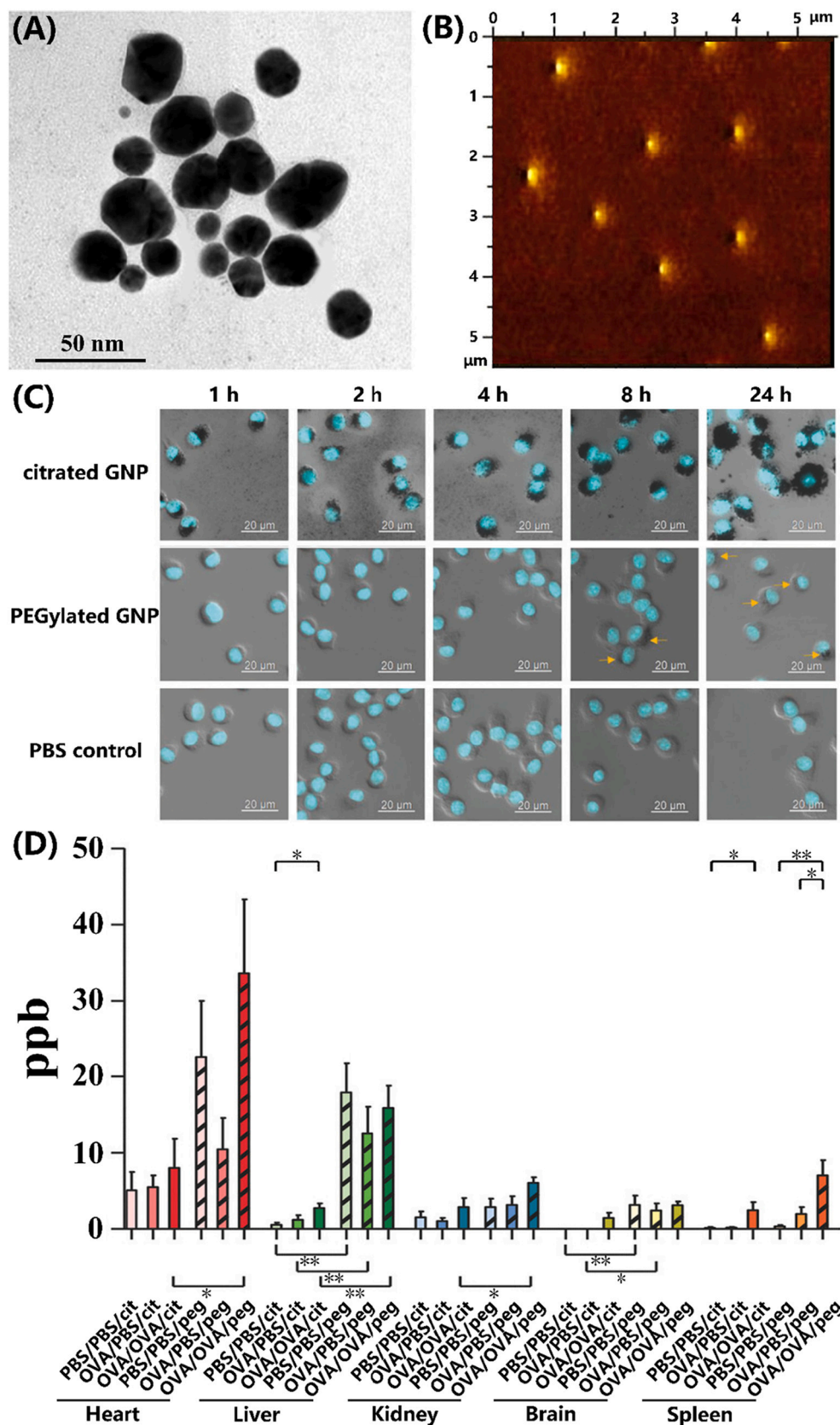


Fig. 4. TEM (A) and AFM (B) images of anti-allergic gold nanoparticles (GNP). Citrated and PEGylated GNP administrated via intranasal route were inclined to be phagocytosed by alveolar macrophages (C), resulting in systemic accumulation (D), especially in heart and liver. Reproduced with permissions from [139,140]. Copyright 2016 John Wiley & Sons, 2019 Elsevier.

verified to be potent in promoting DC maturation and intake, therefore, could be easily recognized and captured by activated immune cells to achieve direct cells damage. Besides, it was reported that the low dose of conjugated OVA onto nano-platform could modulate the bias of Th cells, and help to induce strong and long-acting immune tolerance, which may further reduce Th₂ cytokine (IL-4 and IL-5) release (Fig. 5A) [157]. It was confirmed by Mo that exposure to OVA alone decreased the immune-suppressive Treg cell numbers in airway, while OVA administered with A20, a ubiquitin E3 ligase, significantly suppressed the asthma responses by contrast with the apparent unavailability treated with A20 alone. PLGA-OVA-A20 nano vaccine can effectively improve systemic and mucosal immunity and up-regulate the generation of Treg cells and IL-10 to reverse the skewed Th₂ response, thus achieving allergic inhibitory effect [161].

Chitin, a natural polysaccharide derived from exoskeleton of crustaceans (shrimp, crab, lobster, etc.), insect cuticles, and fungi cell walls, has extensive applications in medical, cosmetic, and environmental industries [60,162–164]. When delivered in the form of chitin microparticles (CMP), it seems to act as potent immune cell adjuvant and macrophage stimulator, which could shift polarization of Th₂ immune responses towards Th₁ type [165]. Phagocytosed CMP triggers effective microbes and granules elimination, and induces Th₁ cytokines (IL-12, IL-18, TNF- α , etc.) secretion to up-regulate Th₁-associated immune responses while down-regulate Th₂-associated ones synergistically for effective anti-allergic curative effect [166]. The validity of CMP was testified in allergic asthma models induced by *Dermatophagoides pteronyssinus*, one of the main dust mites, and *Aspergillus fumigatus*, a ubiquitous fungus inducing hypersensitivity [167]. Encouragingly, CMP reduced serum IgE, peripheral blood and lung eosinophilia, and airway hyper-responsiveness via modulating the Th₁/Th₂ immune response redirection, proven by secretion promotion in Th₁ cytokines such as IL-12, IFN- γ , and TNF- α in spleens. Likewise, the anti-allergic effect of CMP in neonatal allergic asthma mice was detected [168]. After prophylactical utilization of CMP, histopathologic damage, goblet cells over-infiltration, enhanced thicknesses of epithelium, basement membrane, and subepithelial smooth muscle layers were significantly ameliorated, revealing beneficial effect in relieving airways damage. Taken together, the regulation of Th₁/Th₂ immune balance with CMP may offer an innovative and long-acting approach to treat allergic diseases.

As primary contributors to regulating immunity and tolerance, DCs are the key effector cells in immune interventions [169,170]. Direct targeting of antigens to the surface receptors on DCs, such as DEC-205, DC-SIGN, Mannose Receptor, and Clec9a, leads to specifically augmented DCs uptake, presenting and processing [171]. Particularly, the specific targeting of antigens towards DEC-205 induces partial activation or maturation of DCs in the absence of adjuvants, triggering immune tolerance [172–175]. Specifically, Adenoviral vector, Th₁ polarizing agents, has been verified to induce the intra-mucosal production of the Th₁ cytokine such as IFN- γ [176], or the upstream acting of IL-18 [177], and IL-28A [178], which stably reduces the secretion of Th₂ cytokines. Adenovirus was applied as vaccine carrier to induce allergen-specific *in vivo* mucosal expression of fusion proteins, consisting of OVA coupled to single-chain antibody against DEC-205 (Ad-Dec-OVA) for specific DC-targeting immunotherapy (Fig. 5B) [179]. A single dose of intranasal vaccination was effective to reduce OVA-specific IgE and Th₂ cytokines secretion, ameliorate OVA-dependent asthmatic phenotype, and mitigate lung damage in a murine model. The vaccination reduced the Th₂ polarization without resulting in deleterious Th₁ mediated inflammation, proven by the absence of IFN- γ , and OVA-specific IgG2a titers, which broadened the utilities of other vectors inducing in constant antigen levels via mucosal delivery in future studies.

6. Paradigms of airway allergy interventions involving micro/nano-platform

Allergic rhinitis and allergic asthma are two common airway inflammatory diseases. Their pathogenesis has been studied and the treatment of the two diseases has been explored [180]. There are many studies on the application of micro nano system in the treatment of these two diseases, which shows its potential in the treatment of airway allergy.

6.1. Allergic rhinitis intervention

Allergic rhinitis is an upper airway inflammatory disorder with high prevalence, and the symptoms is mainly described as nasal congestion, rhinorrhea, and pruritus, caused by inflammatory process and mucosal dysfunction [181,182]. Sleep deficiency is also involved, accompanied with undesirable behavioral and psychological performances, which brings tremendous adverse effects by interfering intelligence as well as work productivity [183–185]. Local nasal therapy appears to be booming therapeutics to avoid systemic side effects, and meanwhile, intranasal drug administration combined with micro/nano-platform are springing up. For example, chitosan-IL-5 related oligodeoxynucleotide condensed composites were generated, in which chitosan was served as a biocompatible cationic vector to augment transfection efficiency, to regulate secretion of IL-5, and to ameliorate allergic responses [54]. Combined with chitosan provided considerable protective effect of cargo from being enzymatic degraded in conducting airway, and elevated *in vitro* transfection into H1299 epithelial cells compared with naked oligodeoxynucleotide. IL-5 content closely related to allergy was significantly depleted after intranasal administration of condensed complexes (58%) in murine model, and analogous outcomes appeared in IgE secretion and histological findings. Thus, gene therapy associated with chitosan to form therapeutic nanocomplex can serve as effective strategy in alleviating IL-5 related allergic disorders. Moreover, biocompatible poly (methacrylic acid) (PMAA) nanogel was fabricated to load anti-IL-1 β immunoglobulin of yolk (IgY) to combat original proinflammatory mediator IL-1 β , which is a potent acute inflammation inducer [186]. Effective IgY loading (113.6 μ g/mg) and up to 7-day's *in vitro* sustained release (90%) was confirmed. In the guinea pig model with allergic rhinitis, number of eosinophil cells in nasal lavage fluid and nasal mucosa inclined to increase 8 h post intranasal drip of IgY compared with that after 4 h, by contrast, the numbers continued to decline in IgY/PMAA nanogel group, indicating the long-acting and promising curative effect of nanogel.

6.2. Allergic asthma intervention

Allergic asthma, a lower airway progressive inflammatory disease [181], is induced by exaggerated immune cascade responses to extrinsic invasive allergens [187]. The typical syndrome of allergic asthma contains wheezing, chest stuffiness, reversible airway obstruction, airway, and lung hyperresponsiveness [188,189], affecting both children and adults especially in developed countries [190]. Novel therapeutics involving micro/nano-platform to achieve allergic asthma interventions are emerging and present distinct and irreplaceable potential. The anti-asthma effect of budesonide incorporated phosphatidyl-glycerol-phosphatidylcholine-poly (ethylene glycol)-distearoylphosphatidylethanolamine-cholesterol liposomes were determined via weekly aerosol administration compared to daily budesonide therapy in allergic asthma model [191]. Encouragingly, weekly budesonide encapsulated liposomes presented comparable therapeutic effect as daily budesonide treatment proven by decreased lung inflammatory markers, eosinophil peroxidase activity, peripheral blood eosinophilia, and serum IgE concentration, offering superior alternative option over standard daily budesonide therapy in allergic asthma with reduced systematic toxicity and improved patient compliance.

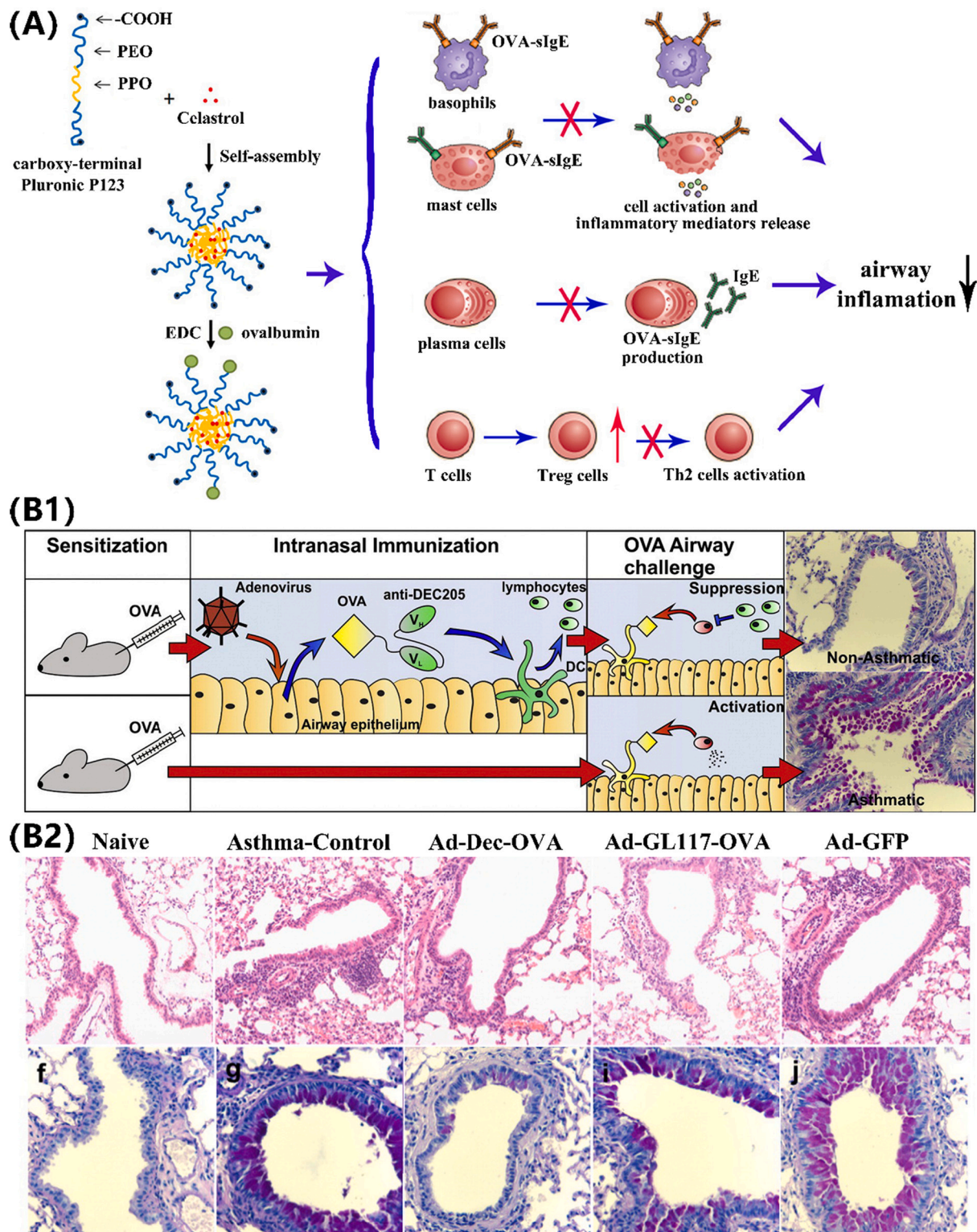


Fig. 5. (A) Scheme of OVA-conjugated nanomicelles with celastrol embedded (OVA-NMs-celastrol), and the anti-allergic mechanism. Coupling OVA to nanomicelles obscured conformational epitopes of Fcε receptor-bound OVA-sIgE, therefore, down-regulating the mediators release from activated effector cells (mast cells and basophils). Antigen-specific antibody titers were maintained by plasma cells and memory B cells. The down-regulated secretion of IgE was attributing to the lack recognition of OVA-NMs-celastrol by memory B cells. Moreover, activation of Treg cells reduced the production of Th₂ cells cytokines, thus reversing the Th bias. (B1) Scheme of intranasal adenovirus vaccine which induced expression of fusion proteins, consisting of OVA and anti-DEC-205 (Ad-Dec-OVA) for specific DC-targeting immunotherapy. (B2) Histological examination of lung stained by H&E (upper panel, indicating eosinophils) and PAS (lower panel, indicating goblet cells) after intranasal immunization with Ad-Dec-OVA, anti-β-galactosidase fused to OVA as control antibody (Ad-GL117-OVA), or GFP as negative control. Ad-Dec-OVA induced intra-mucosal production of Th₁ cytokines and presented satisfactory anti-asthma effect. Reproduced with permissions from [157,179]. Copyright 2016 Elsevier, 2019 Elsevier.

Chitosan-based swellable microparticles were also proposed to achieve sustained budesonide delivery to respiratory tract for local treatment of rodent allergic asthma [46]. After a single administration in murine model, time-dependent suppression of inflammatory cells and cytokines appeared, and curative effect of budesonide incorporated microparticles lasted for 18 h, while micronized budesonide physical

mixture lasted only for 8 h. After successive budesonide embedded microparticles treatment for seven days, the total number of inflammatory cells, IL-4, IL-5 and related mRNA expression, and cells infiltration in peribronchial and perivascular tissues significantly decreased over simple physical mixture. Moreover, the budesonide-chitosan microparticles allowed decreased administrated intervals (every two days) and

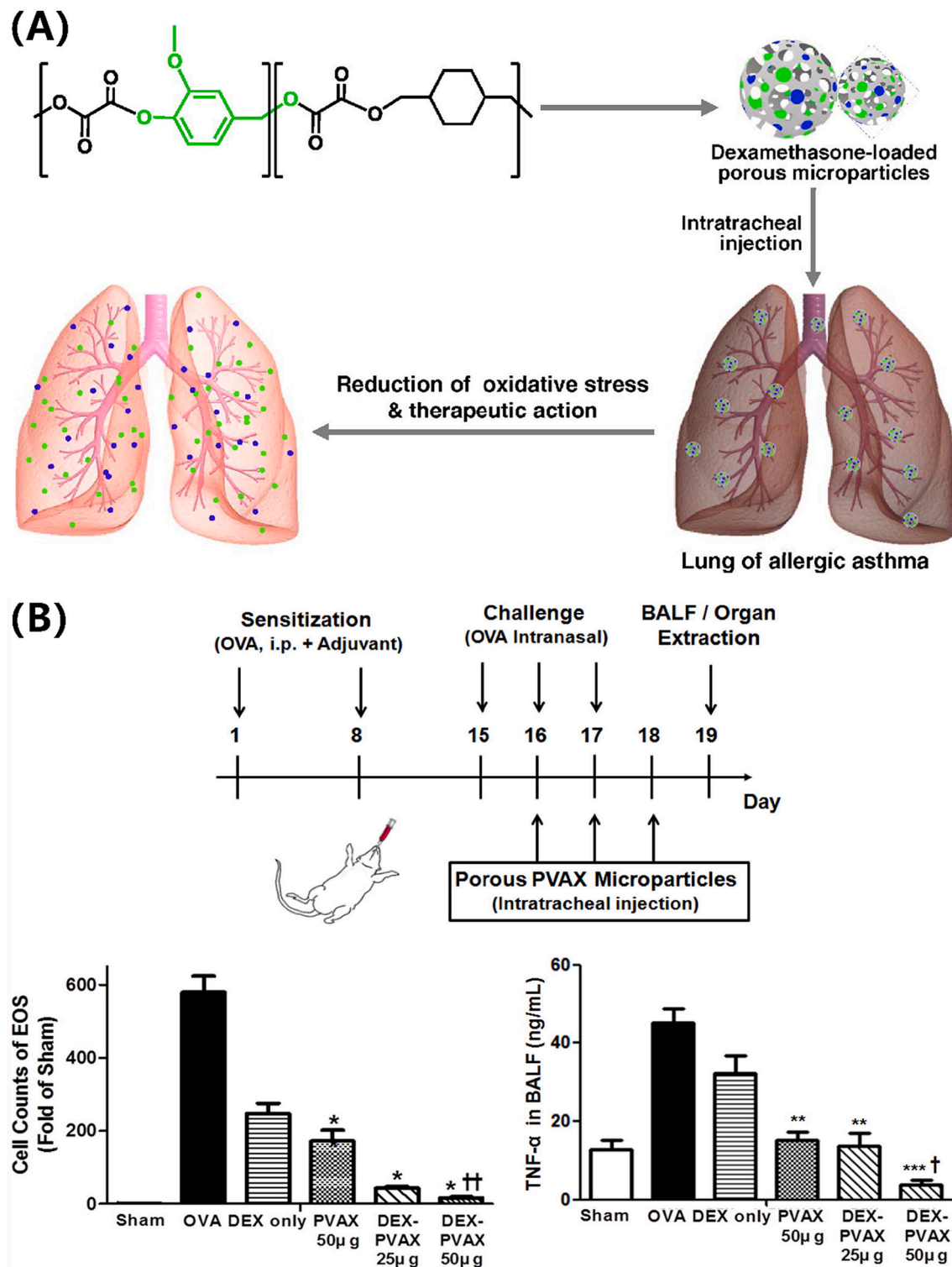


Fig. 6. (A) Scheme of DEX embedded vanillyl alcohol-grafted copolyoxalate (PVAX) porous microparticles for airway inflammatory therapy. (B) Anti-asthmatic efficacy of DEX, PVAX, and DEX-PVAX composites. PVAX microparticles were proven to scavenge hydrogen peroxide, down-regulate oxidative stress, and exert potent anti-oxidant and anti-inflammatory activity, and DEX presented significantly synergistic curative effects with PVAX. Reproduced with permission from [51]. Copyright 2016 Elsevier.

dose (half-dose), demonstrating the sustained curative effectiveness of budesonide delivered via swellable microparticles to lungs, which can be extended to other compounds for local lung diseases therapy. Moreover, the potent anti-allergic effects of vanillyl alcohol-containing copolyoxalate (PVAX) microparticles were verified and applied to prepare polymeric prodrug, with peroxalate ester bonds breaking and vanillyl alcohol releasing triggered by hydrogen peroxide [51]. DEX encapsulated PVAX microparticles presented significantly enhanced curative effectiveness than DEX or PVAX alone, revealing the synergistic effects of PVAX and DEX (Fig. 6). Overall, micro/nano-platform have appeared distinctly prominent superiority in airway allergy management for prolonged residence time, enhanced possibility of low-dose administration, as well as improved anti-allergic effect.

7. Challenges of micro/nano-platform via intratracheal delivery

Intratracheal delivery with many advantages in the treatment of airway allergy, faces challenges brought by the physiological characteristics of airway. Mucociliary clearance, respiratory deposition and macrophage phagocytosis are the main challenges for the respiratory delivery of micro/nano-platform. The design of new micro/nano-platform should consider overcoming these obstacles to achieve better therapeutic effect.

7.1. Mucociliary clearance

Mucous hypersecretion is triggered and regulated by allergen-specific Th₂ cells, which seems to be the key hallmark of respiratory diseases, and subsequently, leading to eosinophilia [192]. Though viscoelastic mucus is much more tenacious in obstructive airway disorders (e.g., cystic fibrosis, chronic obstructive pulmonary disease) than in nonobstructive diseases (e.g., allergy, lung cancer) [193], micro/nano-platform to combat airway allergy via intratracheal route still need to be delicately designed to bypass the capture and elimination by respiratory mucus, or the micro/nano-platform will be sequestered and excreted via cough [194]. Meanwhile, regular movement towards the nasopharynx region driven by the widely distributed cilium system along respiratory tract results in rapid clearance of inhaled granules, either [195,196]. Particle diameters and surface modifications are crucial for micro/nano-platform to stride across mucociliary barriers. Micro/nano-platform with relatively smaller sizes are more likely to escape from cilium barrier, and diffuse through low viscosity mucus fiber biopolymer networks [197]. Micro/nano-platform with negative or neutral surface charge and hydrophilic modification such as PEGylation, are supposed to stride the mucociliary clearance barrier [198,199].

Moreover, mucoadhesive micro/nano-platform and micro/nano gelling agents which can provide targeted localization and intensified interaction with respiratory mucosa, thus increasing the therapeutics concentration gradient and prolonging drug retention, are also feasible orientation [200]. For example, bioadhesive starch/cyclodextrin microsystem was assembled and employed as intranasal administrated platform for Gabexate Mesylate (Foy's, inhibitor of trypsin) delivery to combat allergic rhinitis [48]. Though the microspheres presented relatively rapid cargos release within 1 h, such particles would potentially serve as satisfactory platforms for nasal administration as they can adhere to nasal mucosa tightly to prolong local retention.

7.2. Respiratory tract deposition

Compared to nasal cavity targeted delivery, pulmonary delivery seems to face severer challenge, as the deposition position of the granules is uncertain [201–203]. Inertial impaction, sedimentation, and diffusion are three key factors affecting the deposition position of micro/nanoparticles in respiratory tract [204,205]. For effective pulmonary delivery, the particles should possess aerodynamic diameters of 1–5 μm in order to pass through the mouth, throat, conducting airway, and

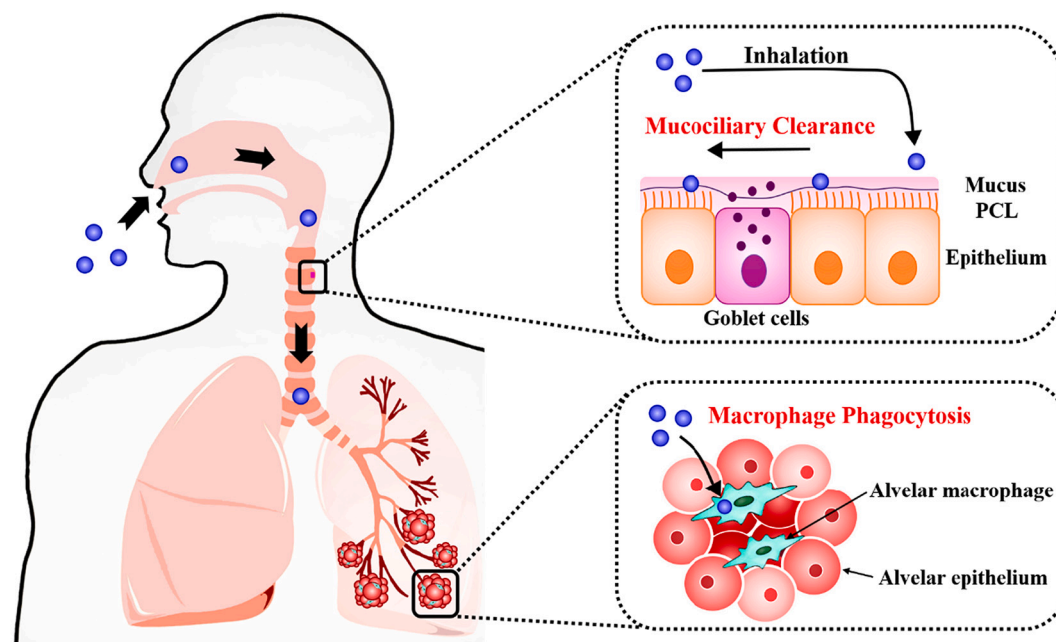
bronchiole to finally reach and deposit in the area of deep lung, via inertial impaction [206,207]. Droplet sizes for aerosols smaller than 1 μm display Brownian motion in conducting airway, and are likely to be exhaled rapidly [208,209]. Microparticles with diameters more than 5 μm are more likely to reach the upper airway and nasopharynx areas by virtue of greater gravitation and inertia, leading to subsequently swallowed into the gastrointestinal tract and eliminated along with sputum [210]. The deposition is also affected by a battery of factors like microsystems density, hygroscopicity, and shapes. Particles with densities of 0.4 g/cm^3 and geometric sizes of 20 μm are the cut-off limits for efficient pulmonary deposition [211]. Considering the complicatedness of the deposition behavior, detailed explorations of aerodynamic behavior and sedimentation dynamics of a certain kind of microparticles are of vital importance.

7.3. Macrophage phagocytosis

Besides these two above challenges, how to avoid phagocytosis by alveolar macrophages after lung deposition is also a major challenge (Scheme 3) [212]. Respiratory tract targeted micro/nano-platform are vulnerable to be recognized and phagocytosed by reticuloendothelial system (RES), like alveolar macrophages in topical pulmonary delivery [213–215]. The relatively larger scales, the net positively charged surfaces, as well as the hydrophobicity of the delivery systems, are more likely to trigger the RES recognition [216]. Particles with density of $\sim 1 \text{ g}/\text{cm}^3$ and droplet sizes of 1–3 μm , as mentioned above, are optimal for lung deposition, while incline to be phagocytosed by alveolar macrophages [211], thus, delicate, and rational design for delivery system is imperative. Nano-sized delivery system is proven to effectively escape from premature RES phagocytosis, while it is vulnerable to be exhaled due to its extremely low mass, delivering via forms of colloidal suspension, formulating nano-platform into inhalable micro-aggregates, or establishing sizes adjustable swellable systems, seems to be feasible paths to achieve both respiratory deposition and avoid macrophage phagocytosis [217]. Recently, porous swellable micro/nano-platform with size ranges suitable for respiratory inhalation before swelling to notably larger sizes once in contact with the pulmonary fluid, have attracted much more focus as they can effectively deposit and elude macrophage uptake in deep lungs [46,206]. Furthermore, like the mucociliary evasion approach, PEGylation which can shield positive surface charge and reverse the hydrophobicity, as well as mucoadhesive functionalization which can enhance the interaction and delay elimination [218,219], safeguard micro/nano-platform against clearance by alveolar macrophages in deep lung [199].

Despite RES evasion is treated as dominating challenge for intratracheal delivery route, micro/nano-platform uptake by alveolar macrophages may reveal advantageous effects in certain conditions [214,220]. For example, betamethasone phosphate (BMP) loaded fluorescent nanoparticles were verified to be internalized in vesicles of peribronchial and alveolar M2 macrophages, and the macrophages can serve as BMP reservoirs for gradual releasing into surrounding matrix and acting on receiver-cells, thus, conferring nano-platform with satisfactory anti-allergic effects [50].

Taken all these above, it is necessary for the micro/nano-platform to be size-proper, biocompatible, biodegradable, evasive from mucociliary resistance, and macrophage phagocytosis, capable for target site deposition and sustained local cargo release. Ideal intratracheal targeted micro/nano-platform should be equipped with appropriate “strategies” to overcome most, if not all, of the obstacles. Nowadays, synchronized attempts to formulate micro/nano-platform to serve as delivery vehicles, therapeutics, and immunomodulators in airway allergy interventions have been proposed to overcome these existing pathophysiologic barriers.



Scheme 3. Diagram of the respiratory tract and challenges of micro/nano-platform via intratracheal delivery, graphics on the right are magnified cartoon images of tissue structure barriers of conducting airway (upper) and alveoli region (lower). The mucosal tissue of respiratory tract consists of ciliated epithelium, mucus-secreting goblet cells, mucus and periciliary layer (PCL), which can eliminate inhaled granules via upward mucociliary movement. Once the granules finally reach the alveoli region, they also face the recognition, phagocytosis, and clearance by alveolar macrophages, leading to the consequent cellular and humoral immune responses.

8. Conclusions and outlook

The application of micro/nano-platform in the management of airway allergy through airway pathway has greatly improved pharmacotherapy and immunotherapy widely used in clinic, and it is a potential delivery method. Researches on advances in therapeutic drugs or bioactive molecules have recently been presented, providing innovative managements to cure excessive immune responses attributing to all-sided and in-depth understandings of etiopathology, which can also be adopted in airway allergy intervention [221]. In addition to conventional chemotherapeutics, peptides, nucleic acids, and bioactive molecules have been developed for the treatment of airway allergy. Intratracheal administration enhances local drug concentration while facing the challenges of low drug absorption, rapid clearance, and easy degradation. The practical benefits of micro/nano systems against allergic airway inflammation have been highlighted for escaping from mucociliary clearance, protecting payload from being inactivated, degraded, and phagocytosed, enhancing local retention and permeation, reducing systematic side effects, and broadening disease therapeutic options [222,223]. We systematically introduce the application of micro/nano-platform as drug delivery carrier in airway allergy, including enhancing drug specificity, efficacy, and accessibility, while reducing systemic toxicity. The function of micro/nano-platform as therapeutic agent and immunomodulator contributes to the synergistic treatment of airway allergy. Nevertheless, the emerged functions of micro/nano-platform in airway allergy managements almost focus on the roles as delivery vehicles, researches on advanced micro/nano-platform as therapeutics and immunomodulators need further explorations. Ongoing efforts are meanwhile necessary to clearly identify the mechanisms of existing curative micro/nano-platform such as nano noble metal, also to overcome the complicated preparation and modification process of partial formulations [140,149,224]. The deepening of the functional research of micro/nano-platform in treatment and immune regulation will make it possible to design more simple and efficient delivery carriers.

The further improvement of delivery effect of micro/nano-platform

is hindered by mucociliary clearance, respiratory tract deposition and macrophage phagocytosis. The safety of micro/nano-platform, including biocompatibility, degradability, immunogenicity, and the permeability of blood-brain barrier, also need to be considered. Various carrier improvement strategies, including PEGylation, chemical modification and characterization optimization, have been proposed to enhance the delivery capacity of micro/nano-platform. The stability and residence time can be improved by chemical modification of the delivery carrier, such as covalently connecting polyethylene glycol [225]. The development of derivatives of chitosan, such as hydroxybutyl chitosan, can improve its solubility and reduce toxicity [60]. Smaller particle size and near neutral surface charge may be more favorable for drug delivery [226]. The combination of polycation nanoparticles and polyanion nanoparticles can effectively improve the stability of nanoparticles and reduce the toxicity of polycation. The conditions for the formation of nanoparticles by electrostatic interaction are mild.

With the development of immunotherapy in airway allergy, the influence of micro/nano-platform on antigen induced immune tolerance will become a potential direction. Moreover, micro/nano-platform with real-time fluorescent imaging characters as synchronous management strategies might be promising orientations to achieve visual location, drug tracing as well as effective diseases control [227,228]. Following these future perspectives, the to-be intratracheal delivered micro/nano-platform will become more promising candidates or alternatives for local or even systematic allergy therapy strategy.

Declaration of Competing Interest

There are no conflicts to declare.

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