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Current possibilities and future perspectives for improving efficacy of allergen-specific sublingual immunotherapy

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ABSTRACT

Allergen-specific sublingual immunotherapy (SLIT), a safe and efficient route for treating type I hypersensitivity disorders, requires high doses of allergens. SLIT is generally performed without adjuvants and delivery systems. Therefore, allergen formulation with appropriate presentation platforms results in improved allergen availability, targeting the immune cells, inducing regulatory immune responses, and enhancing immunotherapy's efficacy while decreasing the dose of the allergen. In this review, we discuss the adjuvants and delivery systems that have been applied as allergen-presentation platforms for SLIT. These adjuvants include TLRs ligands, 1α, 25-dihydroxy vitamin D3, galectin-9, probiotic and bacterial components that provoke allergen-specific helper type-1 T lymphocytes (TH1), and regulatory T cells (Tregs). Another approach is encapsulation or adsorption of the allergens into a particulate vector system to facilitate allergen capture by tolerogenic dendritic cells. Also, we proposed strategies to increasing the efficacy of SLIT via new immunopotentiators and carrier systems in the future.

1. Introduction

Sublingual immunotherapy (SLIT) was introduced as a non-invasive and safe approach for type I hypersensitivities and has recently emerged as an exciting alternative for subcutaneous immunotherapy (SCIT) with fewer systemic adverse events. This approach has been conducted using aqueous allergen extracts or solid tablets sublingually [1–3].

When allergens are administered in this route, the primary target cells are Langerhans cells (LC). They are located within the mucosa as local antigen-presenting cells (APCs) and can uptake allergens. Other APCs, including lamina properia resident myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs), capture the allergens in the submucosa region. These cells migrate to the draining lymph nodes where they can present epitopes of allergen to naïve CD4 + and CD8 + T cells to induce their differentiation into effector helper (TH) and cytotoxic T lymphocytes (CTL), therefore trigger the immune responses [4].

SLIT motivate the immune responses in the allergic person to polarize from the TH2 phenotype (pro-allergic IL-4, IL-5, IL-13, IL-10 and IL-6 producing $CD4^+$ T cells) to the TH1 (IFN-γ and IL-2 secreting cells), and regulatory T cells (TGF-β and IL-10 secreting cells) [5–7]. (Fig. 1)

Generally, SLIT is accomplished in an adjuvant-free route, therefore requires high doses (50–100 times higher in comparison to SCIT) of allergen extracts to reach a sufficient clinical efficacy [8]. Allergens can be administered with immune modifying agents and vector systems to target oral DCs more efficiently and inducing proper modulatory immune responses. The efficacy of SLIT should improve by enhancing the allergen-presentation platforms and reducing the administered allergen dose [9].

This review focused on conventional adjuvants and delivery systems combined with the allergen(s) to enhance the efficacy of sublingual allergy vaccines. Also, strategies proposed that can be considered as candidates for future allergen delivery in SLIT.

2. Adjuvants

The immunomodulatory and immune-modifying properties of adjuvants made them an exciting strategy to promote the safety and efficacy

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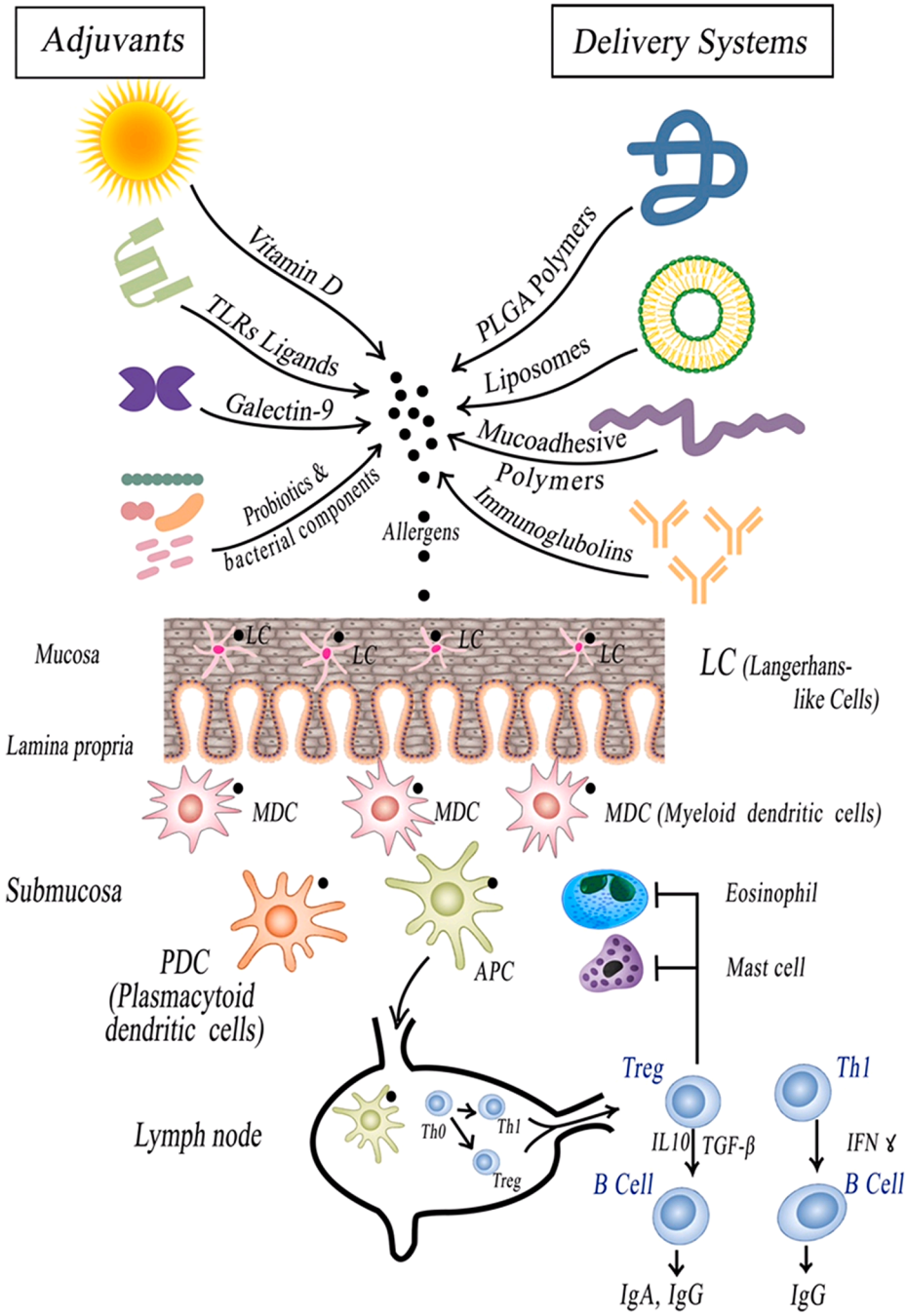

Fig. 1. A schematic presentation of adjuvants and delivery systems in improving SLIT efficacy. The combination of allergens with carrier systems and immunopotentiator agents for SLIT resulted in the capture of allergen by oral LCs within the mucosa and other APCs in lamina propria submucosa. Then APC migrates to the lymph node and presents allergens to naïve T cells (TH0) to induce the differentiation into the helper and regulatory T cells. These polarized cells participate in IgG and IgA production and IgE suppression.

of allergen-specific immunotherapy (SIT) when administrated in combination with allergens decreased allergen doses administration as well as reducing side effects resulted from IgE-allergen complex formation [10]. Adjuvants that have been used in SLIT so far include TLRs ligands, vitamin D, galectin-9, probiotics, and bacterial products. (Table.1)

2.1. TLRs ligands

Toll-like receptors (TLRs) are a type of pathogen recognition receptors (PRRs) that belong to the innate immune system receptors, which are expressed on different types of cells and play a critical role in recognizing pathogen-associated molecular patterns (PAMPs). It demonstrated that administration of TLR agonists as an adjuvant have therapeutic and prophylactic effects on asthma and allergic rhinitis (AR) patients [18].

2.1.1. TLR2 agonist

Lombardi et al. administered three TLR2 ligands (*Porphyromonas gingivalis* lipopolysaccharide, lipoteichoic acid (LTA) Pam3CSK4) sublingually to the OVA-sensitized murine. They also treated DCs with these adjuvants and then co-cultured with naïve CD4 + T lymphocyte. This study showed that only Pam3CSK4-treated DCs could induce IL-10 and IFN-γ production in naïve CD4 + T cells and co-administering Pam3CSK4 OVA via the SLIT route could considerably decrease the airway hypersensitivity and TH2 responses. These results show that Pam3CSK4 may act as an anti-allergic agent [11].

2.1.2. TLR4 agonist

TLR4 is expressed on oral Langerhans cells (oLCs), and as mentioned earlier, these APCs are the most critical targets in SLIT. In an *in-vitro* study, Allam and colleagues showed that when oLCs cell suspension

Table 1
List of adjuvants applied so far for SLIT.

Adjuvant		Study Phase/Species		Allergen	Results	Dosage and duration of the treatment	Ref.
TLR agonists	TLR2 agonist (Pam3CSK4)	Pre-clinical	Balb/c	OVA	↑ TH1/Treg responses/↓ AHR and suppressing TH2 activity	8 weeks/500 μg OVA with or without 10 μg Pam3CSK4 in 50 μl PBS	[11]
	TLR9 agonist (CpG-ODNs)		Balb/c	OVA	↑ IFNγ and IgG2a levels/suppressing IgE production	63 days/20 μg OVA combined with 1 μg CpG in 1.2 μl PBS	[12]
	TLR4 agonist (MPL)	Clinical	Human	Grass pollen (Phl p 1)	Negative NCTs after 10 weeks in active-treated patient compare to placebo group/Increasing specific IgG and IgE level	8 weeks/3groups including: 9.45 μg of Phl p 1 + 21 μg of MPL/ 9.45 μg of Phl p 1 + 52.5 μg of MPL/19.04 μg of Phl p 1 + 52.5 μg of MPL	[13]
Vitamin D		Clinical	Human	Grass pollen	↓ Nasal and asthma symptoms/No significance difference between placebo and vitamin D group in the ocular scores	8 weeks/Oralair 300 IR tablet (extract of five grasspollens) with 1000 IU vitamin D	[14]
Galectin-9		Pre-clinical	Balb/c	Df extract	↓ AHR, EAR and serum IgE levels/↑ TGF-β levels	2 weeks/250 μg Df with Gal 9 (0.1, 0.3, or 1.0 μg)	[15]
Probiotics	*L.helveticus*	Pre-clinical and clinical	Balb/c and human DCs and $CD4^+$ naïve T cells	OVA	IL-12p70 and IL-10 induction in DCs/ IL-10 and IFN-γ production in $CD4^+$ T cells/↓ AHR and TH2 responses/↑ Tregs and TH1	8 weeks/500 μg OVA with live probiotic bacteria in 50 μl PBS	[16]
	B.bifidum NC453		Balb/c mice, human DCs and allogeneic $CD4^+$ naïve T cells	rBet v 1 and OVA	Inducing DC maturation/↑ IFNγ and T-bet gene expression/↑ Tregs cells/↓ AHR and TH2 responses	8 weeks/50 μg Bet v1 with or without *B. bifidum* in 20 μl PBS	[17]
Cholera toxin (CT)		Pre-clinical	Balb/c	OVA	Enhancing IgG1 and IgA levels/No suppression in IgE levels	63 days/20 μg OVA combined with 0.2 μg CT in 1.2 μl PBS	[12]

Abbreviations: OVA, ovalbumin; **AHR**, airway hyper-responsiveness; **MPL**, monophosphoryl lipid A; **NCT**, nasal challenge tests; **CpG-ODNs**, CPG oligodeoxynucleotides; **Df**, *Dermatophagoides farinae;* **EAR**, early asthmatic response; **Gal 9**, galectin 9; **Phl p 1,** *Phleum pratense* 1; **PBS**, phosphate-buffered saline.

is obtained from oral mucus trypsinization, encountered with MPL (TLR4 agonist), co-inhibitory molecules expressions (i.e., B7-H1 and B7-H3) were increased. In contrast, the expression of CD86 as a co-stimulatory molecule was decreased. The TLR4 ligation on oLCs resulted in IL-10, TGF-β1, IL-12, and IFN-γ secretion. Furthermore, it contributes to TH subsets shift to TH1 and the development of the tolerogenic condition in the oral cavity [19].

Another study also demonstrated that OM-294-BA-MP as well as OM-197-MP-AC, synthetic and non-toxic pseudo-dipeptide analogs of lipid A, improved the efficacy of SLIT in a murine model of allergy through induction of TH1/Tregs responses and affect AHR and lung inflammation [20].

Pfaar et al. administrated MPL as an adjuvant for SLIT in a clinical trial for the first time. Results showed lower adverse reactions, better nasal challenge tests (NCTs) outcomes, and more efficient IgE reduction. An increase in the IgG levels in the group received SLIT with the highest MPL content compared to the placebo group after ten weeks [13]. These data demonstrated that MPL-adjuvanted SLIT could promote tolerance in grass pollen-sensitive patients.

2.1.3. TLR9 agonist

CpG oligodeoxynucleotides (CpG-ODNs) have been described as immune-stimulatory ligands of TLR9, an endosomal TLR APCs, and their interaction leads to the secretion of cytokines including IFN-γ and IL-12 that are necessary for TH1 polarization in allergic patients [21]. After sensitization of newborn Balb/c mice which sublingually vaccinated with OVA or CM-OVA + CpG, the secretion of IFN-γ in the spleen and cervical lymph node (CLN) cells and production of IgG2a antibody responses enhanced, while IgE responses significantly suppressed [12].

2.2. Vitamin D

The calcitriol (the synthetic form of 1α, 25-dihydroxy vitamin D3) is an active metabolite of vitamin D associated with immune responses involved in the allergy. The Vitamin D receptor activation can improve IL-10 gene expression and inhibit IgE production in B cells [22]. In patients resistant to steroids, calcitriol plus therapy has induced IL-10-producing T cells differentiation and enhanced lung function [23]. Also, vitamin D's co-administration in an allergen-specific immunotherapy procedure could decrease airway inflammation and TH2 cytokines expression [22].

The vitamin D supplements combined with SLIT induced well-tolerated and effective responses in children with allergic rhinitis. In the vitamin D-treated groups, nasal and asthma symptoms had significantly fallen compared to placebo groups when SLIT performed coincidently with vitamin D administration [14]. Also, it was observed that vitamin D3 combined with dexamethasone could polarize CD4 + T lymphocytes to the IL-10-producing T cells and improved SLIT efficacy in animal models [24].

2.3. Galectin 9

Galectin-9 (Gal-9) is a membrane protein that specifically binds to the β-galactoside residues and participates in immunologic reactions, which leads to the Tregs and immunosuppressive macrophages induction and inhibits TH17 and TH1 polarization [25,26]. This protein could induce apoptosis in TH1 and TH17 subsets by binding to Tim-3, leading to an improvement of autoimmune conditions [25]. Also, it has been observed that interaction between Gal-9 and CD44 augments stability and function of adaptive or induced Treg (iTreg) cells [27]. In the presence of Gal-9, sublingual immunotherapy with *Dermatophagoides farinae* (Df) in chronic asthma mouse model notably decreased Airway hyper-responsiveness (AHR), IgE levels, Early asthmatic response (EAR), number of eosinophils and IL-13 levels in the Broncho-alveolar lavage fluid (BALF), while increased TGF-β levels. Gal-9 enhanced the SLIT efficacy as a novel adjuvant in asthmatic models [15].

2.4. Probiotics

World Health Organization (WHO) defined probiotics as "live microorganisms that have generally been considered safe to consume and provide health benefits for the host". Such microorganisms seem to have immunomodulatory effects on dendritic cells and T lymphocytes functions and reduce inflammatory responses induced by food allergens. The *Lactobacilli* and *Bifidobacterium* are the most common bacterial species administered in animal models and human clinical trials [28–31].

Eleven different lactic acid bacteria strains were administrated in combination with SLIT in the murine asthma model. Results have shown that *Lactobacillus helveticus* induces IL-12p70 and IL-10 secretion in DCs

Table 2
List of delivery systems so far applied for SLIT.

Delivery system		Study Phase/	Species	Allergen	Results	Properties/safety	Dosage and duration of treatment	Ref.
Nanoparticle-based systems	PLGA	Pre-clinical	Balb/c	rChe a 3	↓ IL-4 and IL-13 expression/↑ IFN-γ and IL-10 secretion/ enhancing IgG2a levels/no significant changes in the IgG1 or IgE levels	Most commonly used polymers, FDA approved, biodegradable, biocompatible, well-tolerated, cleared through the tricarboxylic acid cycle	8 weeks/100 μg of rChe a 3 plus PLGA nanoparticles (at 5, 25, or 50 μg/dose) in a total volume of 25 μl	[37]
			Balb/c	OVA	↓ IgE level and IL-4, and IL-17 secretion/ ↑ TGF-β, IL-10, and IFN-γ levels/ improved lung inflammation and reduced leukocyte counts		8 weeks/10 and 5 μg of Ova per dose encapsulated in PLGA	[38]
			Balb/c	OVA and CUR	Improved lung inflammation and reduced leukocyte and eosinophil counts in BALF/ ↓ IL-4, secretion and ↑ IFN-γ levels		8 weeks/5 μg OVA and 5 or 10 μg CUR encapsulated in PLGA	[39]
	GNPs		Balb/c	OVA	↓ IgE level and IL-4 secretion/ ↑ TGF-β, and IFN-γ levels/ improved lung inflammation and reduced leukocyte and eosinophil counts in BALF	Unique electric and optical properties, low toxicity, tunable size, high affinity with thiol groups	8 weeks/GNPs containing 5 μg OVA	[40]
	liposome		Balb/c	OVA	↓ IgE levels and Eosinophil percentage in BAL liquid/↓ IL-4, IL-5 and IL-10/no changes in IL-13 levels	Biocompatible, biodegradable, not toxic, non-immunogenic. high cost to produce, short half-life and low solubility in water are its disadvantages	39 days/50 μg of OVA-liposomes	[3]
Mucoadhesive-based systems	chitosan	Pre-clinical	Balb/c	OVA	↓ IL-5 and IL-13/↓ AHR and eosinophil number	Biodegradable, renewable, water soluble, antibacterial properties and high cost of purification	8 weeks/500 μg/dose chitosan-formulated OVA	[41]
			Balb/c	Df	↑ IFNγ and IL-10/Suppressing IgE/↓ IL-4 level and AHR		18 doses at 1-day intervals/1 mg Df formulated with chitosan nanoparticle	[42]
			Balb/c	Papain	No reduction in Th2 cytokines in BAL fluid/suppressing neutrophilia, IgE and IgG1 antibodies/↑ IFNγ and IL-10 levels.		Not mentioned	[43]
	maltodextrin		Balb/c	OVA	↓ AHR and eosinophil accumulation/No detectable changes in serum IgE and IgG antibodies	Readily dispersible in water	8 weeks/500 μg or 50 μg OVA per dose	[44]
	amylopectin		Balb/c	rBet v 1a	↓ in TH2 cytokines secretion/↓ in eosinophil and AHR	A water-soluble and highly branched polymer	8 weeks/5, 50, 100 and 500 μg rBet v 1a per dose	[45]
Peptide-based system	TAT-PTD	Pre-clinical	Balb/c	rChe a3	↓ IL-4 levels/↑ expression of FoxP3 and TGF-β mRNA/ enhancing IgG2a antibody	–	8 weeks/100 μg/dose of rChe a 3	[46]
APC-targeting-based system	adenylate cyclase	Pre-clinical	Balb/c	OVA	↓AHR, allergen-specific TH2 responses and recruitment of eosinophil in BALF	Specific targeting of oral CD11b^{+} cells	8 weeks/500 μg OVA	[47]

Abbreviation: OVA, ovalbumin; **CUR**, curcumin; **PLGA**, poly (lactic-co-glycolic acid); **rChe a3**, recombinant Chenopodium album3; **GNPs**, gold nanoparticles; **BALF**, bronchoalvelolar lavage fluid; **Df**, Dermatophagoides farinae; **TAT-PTD**, TAT protein transduction domain; **AHR**, airway hyper-responsiveness.

and polarizes IL-10 and IFN-γ producing-T CD4 + lymphocytes. In contrast, *L.casei* has similar effects and provokes TH1 differentiation and activation. Also, AHR, bronchial inflammation, and specific T lymphocyte proliferation diminished when *L.helveticus* administered sublingually in OVA-sensitized mice [16]. Other Lactobacillus species such as *L. Plantarum* enhanced priming of OVA-specific T cells and may induce tolerance via IL-10 secretion by DCs and T cells [24].

Immunomodulatory effects of lactobacillus have been investigated in a human clinical trial enrolled 6–17 aged children with asthma. Significant reduction in the IL-4, IL-5, and IgE levels and increase in the IFN-γ and TGF-β were reported and improvement in the lung function test [29].

Another study conducted by Moussu et al. investigated three *Bifidobacterium* species as adjuvants. They demonstrated that *B. bifidum* NCC453 could shift TH2 response toward Tregs/TH1 patterns and downregulates AHR and lung inflammation. Thus this strain of probiotics is a valid immune-modifier for induction of tolerance in type-1 hypersensitivity by sublingual administration route [17].

The *Lactococcus Lactis* is another probiotic strain used as a live oral vaccine against allergy, which is highly sensitive to the gastrointestinal contents and suffers from low adhesion capacity [32]. Ghasemi et al. revealed that Sal K1-expressing *L.Lactis*, the major allergen of Salsola Kali pollen, acts as a live sublingual vaccine for allergy treatment. They showed the vaccine decreasing IgE and IgG1 levels in serum and IL-4 levels in spleen cells culture supernatant while increasing IgG2a levels in the serum and IL-2, IL-10, IFN-γ, and TGF-β in spleen cells culture supernatant of Balb/c mice [33,34].

2.5. Bacterial products

Cholera toxin (CT), the exotoxin of *Vibrio cholera,* was described as a potential adjuvant due to the immune-stimulatory properties. When CT was administered sublingually to the neonate Balb/c mice, allergen sensitization improved their IgG1 responses only, whereas the IgE levels were not affected. Moreover, CT effectively enhanced IgA mucosal antibody responses [12].

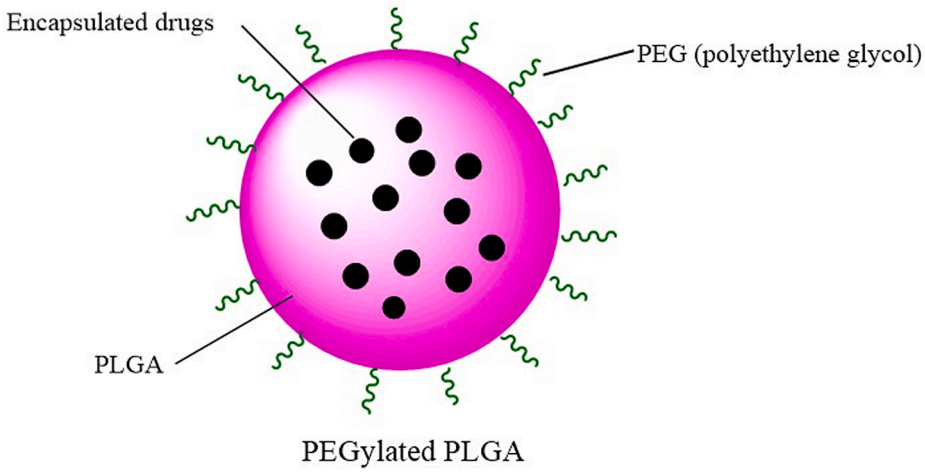

Fig. 2. Schematic description of PEGylated PLGA that encapsulated with drugs.

3. Delivery systems

Vector or delivery systems are used to facilitate allergen uptake by oral APCs by increasing the allergen presence in mucosal surfaces and/or presenting allergen as a particle and enhancing the targeting of allergen to tolerogenic APCs [5,35]. Specifically, mucoadhesive-based carrier systems seem to be well-updated to sublingual or other mucosal routes of allergen administration. They can prolong the exposure duration between allergen and oral mucosa. Also, administrating delivery systems in mucosal routes should preserve allergen from local proteases while targeting APCs. These systems also enhance the immunotherapy efficacy via a decrease of applied dose and modulating appropriate immune cells [36]. These systems are divided into four main categories: nanoparticle-based, mucoadhesive-based, peptide-based, and APC-targeting-based strategies (Table.2).

3.1. Nanoparticle-based systems

Nanoparticles (NPs) are polymeric particles that act as a delivery system for allergens [48]. Allergen encapsulation in NPs results in a protection against enzyme degradation or pH alteration, avoids detection of Antigen by IgE on the surface of mast cells or basophils, and reduces side effects by concealing Allergen from the immune system [49]. PLGA NP, because of its well-established biocompatibility, safety, and biodegradability, has received significant attention for clinical applications in human studies for allergen immunotherapies [50,51]. PLGA has some tunable features, including surface charge, shape, size, hydrophobicity, and hydrophilicity [52]. Optimizing the preparation method to obtain the different sizes of NPs is a critical point because capturing NPs by APCs is mainly dependent on the size of NPs. Recent studies demonstrated that encapsulation and loading efficiency and also successful allergen release profile were closely related to nanoparticle size [53,54]. (Fig. 2)

PLGA polymers were also broadly used as delivery devices for several protein antigens and have been employed for different administration routes [37,55–60]. Sublingual immunotherapy in mice with rChe a 3-encapsulated PLGA NPs improved efficacy of SLIT compared to a free soluble allergen because of TH2 immune responses down-regulation and

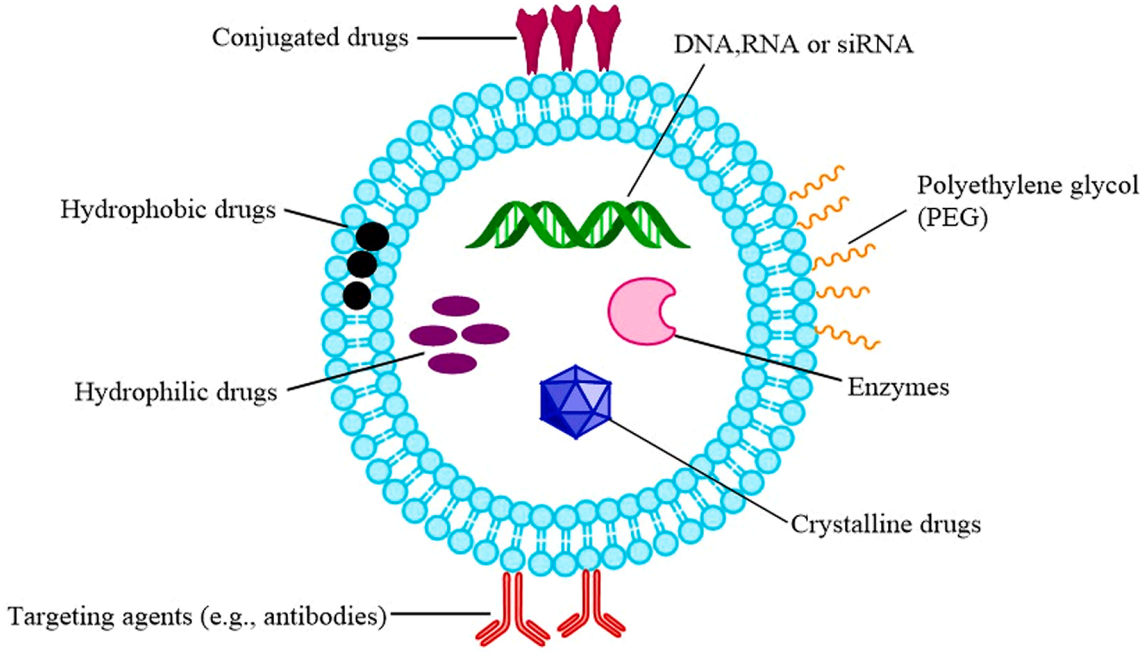

Fig. 3. A schematic representation of liposomal drug delivery system.

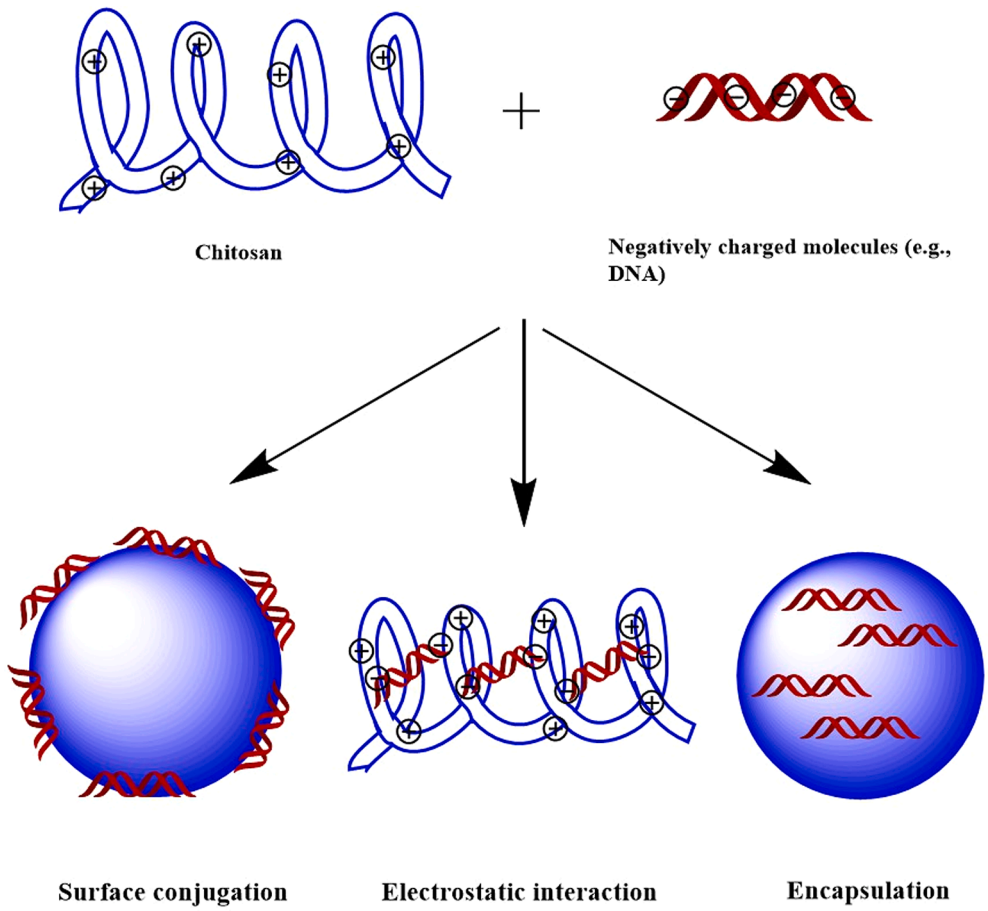

Fig. 4. Applications of chitosan in drug delivery.

established TH1/TH2 balance. Also, PLGA formulation reduced administrated allergen doses and enhanced systemic TH1 and Tregs immune responses [37]. In another study, Keshavarz Shahbaz et al. evaluated the efficacy of OVA-encapsulated PLGA NPs decorated with DCs-specific aptamer. They showed that SLIT with this formulation significantly reduced IgE levels and IL-4 secretion and significantly increased IFN-γ and TGF-β in the murine model of allergy [38]. Also, Shahgordi and colleagues administered PLGA containing OVA, curcumin or both to enhance the efficacy of SLIT in the mouse model of allergic rhinitis. They demonstrated that this formulation significantly increased the IFN-γ: IL-4 ratio while decreased lymphocyte and eosinophil count as well as cellular infiltration and inflammation in nasal lavage fluid and lung tissue, respectively [39].

Gold nanoparticles (GNPs or AuNPs) have been widely studied as a drug delivery agent due to their biodegradability and biocompatibility. The FDA has also approved them for Human Studies. Non-toxicity and availability for surface modifications to target specific molecules or biomarkers are among the most attractive features of these NPs [61,62]. Sadeghi et al. administered DC-specific aptamer-modified GNPs coated with OVA to improve the efficacy of sublingual immunotherapy and reported that while the IL-4 production decreased in spleen cells, significantly increased IFN-γ and IL-10 secretion was seen. The IgE serum level was also reduced in line with decreased leukocyte and eosinophil count in BALF and improved inflammation in lung tissue [40].

The liposome is another NP that has been used in SLIT (3). It is a spherical vesicle with an aqueous solution core surrounded by a lipid bilayer membrane that self-assembled in the aqueous environment. This NP entraps hydrophilic Antigens and acts as an adjuvant and delivery system [63,64]. Aliu and colleagues treated OVA-sensitized mice with sublingually administrated allergen-encapsulated liposome. OVA-liposome prevented IgE secretion, airway inflammation, and pro-inflammatory cytokines production, except IL-13. Moreover, allergen's encapsulation into the PEGylated liposome prolonged Allergen durability in the peripheral tissues and increased Antigen capture by APCs after sublingual administration in mice. Thus, this carrier system can enhance tolerance induction compared to free OVA administration (3). (Fig. 3)

3.2. Mucoadhesive-based systems

Mucoadhesive vectors are another delivery system developed to be administered as allergy vaccines through mucosal (i.e., sublingual) routes [36]. Most polymers used as mucoadhesive are hydrophilic and adherent to buccal mucosa by hydrogen bonding, electrostatic interactions, and van der Waal's bonds [4]. Mucoadhesive formulations made of chitosan, maltodextrin, or amylopectin have been demonstrated to enhance TH1 immune responses and significantly increase the efficacy of immunotherapy [41,44,45]. Also, mucoadhesive NPs are more capable of improving the intestinal absorption of NPs [65].

Chitosan is a biodegradable, well-tolerated, and the most investigated cationic polysaccharide for mucosal vaccine delivery made of the chitin deacetylation [48,66,67]. The application of chitosan-based nanocarriers for SLIT has been reported by several studies [41–43]. Chitosan that incorporating soluble antigens reduced specific TH2 immune responses, eosinophil numbers in BALF, AHR, and lung inflammation and increased IFN-γ and IL-10 secretion [41,42]. In another study, chitosan engagement in the papain-induced asthma murine model resulted in a non-specific decrease in the TH2 immune responses [43]. (Fig. 4)

Table 3
Suggested adjuvants for use in future SLIT procedures.

Adjuvant	Cargo	Results		Administration route	Species	Comments	Ref.
		Immunologic parameters	Clinical parameters				
QS21 (purified form of saponin)	gp-120	Inducing IFN-γ and IL-2 secreting T cells, low levels of IL-5, no detectable IL-4	–	LM	Balb/c mice	FDA approved	[74]
CA074 (inhibitor of cathepsin B)	–	Shift the response from TH2 to TH1, IgG2a and IFN-γ augment, IgE, IL-4 and IgG1 suppression	–	–	Balb/c and DBA/2 mice	Used in experimental Leishmaniosis	[75]
Escherichia coli Nissle1917 (Probiotic)	OVA/ alum	Inhibition of TH2 responses	↓ airway eosinophilia, airway hyper-reactivity and goblet cell metaplasia	I.P	C57BL/6 mice	–	[76]
MALP-2 (TLR2/6 agonist)	–	↑ IFN-γ secretion by DCs	–	–	human DC	–	[77]
	OVA	↓TH2 activity	↓ AHR and eosinophils count	Intra-tracheal	Balb/c mice	–	[78]
Bisacyloxy propyl cysteine polyethylene glycol (BPPcysMPEG)	Timothy grass pollen	TH2 inhibition	↓ Eosinophilic inflammation and AHR	LN	Balb/c mice	Derivate of MALP-2 and capable of stimulating TLR2/6	[79]
BPPcysMPEG	rPhl p5	↓ TH2 response, ↑ IFN-γ and TNFα	↓ Eosinophilia	LN	Balb/c mice	–	[80]
Lipoprotein 1(OprI) (TLR2/4 agonist)	OVA	Inhibition the production of IL-4 and IL-13	↓ airway eosinophilia	LN	C57BL/6 mice	–	[81]
Lipopeptide-CGP40774 (similar to TLR2 agonist)	OVA	Shift toward TH1, ↑ Tregs and ↓ IgE levels	↓ AHR and airway inflammation	LN	Human PBMCs and Balb/c mice	–	[82]
PolyI:C (TLR3 agonist)	OVA	Induction of IL-12 and IL-10 production, ↓ IgE levels	↓ AHR	LV or S.C	Balb/c mice	Used in low doses	[83]
Imiquimod or R837 (TLR7 agonist)	–	↑ IL-10 levels	↓ alveolar MQ and accumulation of DCs and NK cells in the lung tissue	pipet directly onto the shaved skin	C57BL/6 mice	FDA approved	[84]
Resiquimod or R848 or S28463 (TLR7/ 8 agonist)	OVA	Shift toward TH1 and IFN-γ response, ↓ total IgE levels	↓ AHR, airway remodeling and goblet cells hyperplasia, ↓ eosinophils count	Systemic or I.N	Asthmatic murine model	promotion of long-lasting protection from experimental asthma	[85]
9-Benzyl-2-Butoxy-8-Hydroxy Adenine (SA2) (TLR7 agonist)	OVA	↓TH2/TH17 cytokines and ↑ IL-10 levels	↓ AHR and neutrophilia	I.P	C57BL/6 mice	–	[86]
A Z D 8 8 4 8 (TLR7 agonist)	–	–	↓ α_2 macroglobulin in NALF, ↓ mast cell tryptase in seasonal allergic rhinitis, ↓ symptom and medication score	I.N	Clinical trial	Side effects were seen and included influenza-like symptoms, epistaxis, pharyngeal pain, pyrexia, rhinorrhea, nasal blockage or ulcers, malaise and myalgia	[87]
VTX-1463 or VTX-378 (TLR8 agonist)	Grass pollen	–	↓ symptoms and medication scores	I.N	Clinical trial	Good safety and efficacy and in phase I of development status	[88]

Abbreviation: **OVA**, ovalbumin; **QS21**, *Quillaja saponaria*; **MALP2**, macrophage activation lipoprotein 2; **I.M**, intramuscular; **I.P**, intraperitoneal; **I.N**, intranasal; **I.V**, intravenous; **S.C**, subcutaneous; **AHR**, airway hyperresponsiveness; **NALF**, nasal lavage fluid.

Maltodextrin is another mucoadhesive system that used in SLIT. Sublingual application of OVA-formulated maltodextrin polymers for improving mucosal adhesion caused priming of a local mucosal immune system and enhanced tolerance induction [44].

Another vector system that had been investigated for SLIT is amylopectin. Tourdot et al. formulated rBet v 1a allergen in amylopectin micro-particles and sublingually administered it to birch pollen-sensitized mice. They observed that TH2 immune responses decreased significantly and a higher reduction in AHR occurred. Moreover, the construct of allergen with a mucoadhesive vector system reduced allergen's dose and enhanced the onset of efficacy of SLIT with rBet v 1a [45].

3.3. Peptide-based systems

TAT is a regulatory protein expressed by the tat gene in HIV and has a protein transduction domain (PTD) known as cell penetration peptide. Indeed, PTD allows TAT to enter cells through the cell membrane [68,69]. Administration of TAT-PTD in combination with an allergen in animal models indicated that allergic conditions might be suppressed through enhancing systemic Tregs differentiation and facilitating allergen capture and presenting to DCs [46].

3.4. APC-targeting-based systems

The fusion of allergen to vector molecules for stability improvement and facilitating allergen capture by APCs is an exciting strategy to enhance the SLIT efficacy [70]. In OVA-sensitized mice, specific targeting of allergen to oral CD11b + cells by the adenylate cyclase delivery system significantly reduced AHR, allergen-specific TH2 responses, and recruitment of eosinophils in BALs, therefore induced tolerance following SLIT [47].

Table 4
Suggested delivery systems for use in future SLIT procedures.

Adjuvant	Cargo	Results		Administration route	Species	Comments	Ref.
		Immunologic parameters	Clinical parameters				
Poly anhydrides	Peanut protein	nduce balance between TH1 and TH2 responses	–	Oral	C57BL/6 mice	Solubility in organic solution, biodegradable, biocompatibility, low melting point, FDA approved	[89]
Poly ε-caprolactone (PCL)	OVA	↑ IgG1 levels, ↓ IgE and histamine levels	–	LD	Balb/c mice	Biocompatible, biodegradable, high permeability, fast release in body	[90]
Nanoscale emulsions (NE)	OVA	↑ IgG and IgA levels, modulate TH2 response and shift to the TH1/ TH17	–	LN	CD-1 mice	–	[91]
Protamine-based NPs (proticles)	Ara h2 extract + CpG ODNs	↑ IgG2a levels, ↓ IL-5/IFN-γ ratio and IgE levels	No granuloma formation, lower type I skin test reactivity	S.C	Balb/c mice	Natural and biodegradable polymer	[92]
Poly γ-glutamic acid (γ-PGA)	Mixture of γ-PGA NPs and Phleum pratense extract	↑ Proliferation and IL-10 production	–	–	Human DCs *in vitro*	Natural and biodegradable polymer and self-assembly in aqueous solutions	[93]
Neo-glycocomplexes of oxidized mannan and proteins	OVA and papain	Shift from IgE to IgG (specially IgG1)	–	LD	Balb/c mice	Excellent DC-targeting potential	[94]
Carbohydrate-based particles (microsepharose)	Phl p 5b	Shift from IgE to IgG (specially IgG2a)	No granulomatous tissue reactions, ↓ AHR and eosinophil counts in BALF	S.C	Balb/c mice	Biocompatible, well tolerated and prolonged antigen-exposure	[95]
	rFel d1			I.N or S.C	Balb/c mice		[96]
	rFel d1	↑ CD86, IL-8 and TNF-α levels	–	–	Human DCs *in vitro*		[97]
Chitin particles	–	↓ IgE levels and TH2 cytokines, ↑ IFN-γ levels	↓AHR and eosinophil numbers	I.N or orally	Balb/c and C57BL/ 6 mice	Non-toxic, non-allergenic, biodegradable, and biocompatible	[98,99]
Sodium alginate carrier (Conjuvac)	Der p or grass pollen extract	↓ IgE levels, ↑ IgG4 and IgG1 levels	Improvement the nasal obstruction, no systemic reactions or anaphylaxis	S.C	Clinical trial and Balb/c mice	–	[100–102]
Gelatin NP-based CpG	–	↑ IL-10 levels	Allergic symptoms enhancement (respiratory effort, nasal discharge, tracheal secretion, and viscosity)	Inhalation therapy	Horses	Phase I and II-a of development status	[103]
Virus-like particles (VLP) bacteriophage Qb coat protein	CpG	–	↓ Rhino conjunctivitis symptoms, better quality of life score	S.C	Clinical trial	Phase II-b of development status	[104]
	CpG and Der p 1	↑ IgG levels, ↓ IgE levels, shift toward TH1	Reduced allergic asthma and rhinitis symptoms	I.M or S.C	Clinical trial	Phase I/II-a of development status	[105]
	Fel d 1	↑ IgG levels, ↓ IgE levels and inhibition of local mast cells degranulation *in vivo*	No systemic anaphylaxis	S.C	Balb/c mice	Spontaneous assembly	[106]
Adeno-associated virus-like particles	OVA	↑ IgG levels, ↓ IgE levels	No systemic Anaphylaxis *in vitro or in vivo*	S.C	Balb/c mice	Spontaneous assembly	[107]
Dendrosome Den123	Bet v 1 pDNA	↓ IgE levels, ↑ IgG2a and IgG1 levels and ↑ TH1 immune responses	–	S.C	Balb/c mice	–	[108]
Poly propylene sulfide NPs	CpG	Shift toward TH1, ↑ IFN-γ levels, ↓ IL-5, IL-13 and IL-4 levels	↓ Eosinophils in BALF	LN	C57BL/6 mice	–	[109]
Poly ethyleneimine	OVA pDNA	Induction balance between TH1 and TH2	↓ Nasal symptoms	Patch treatment (topically)	Balb/c mice	–	[110]
Poly vinylpyrrolidone (PVP) NPs	Aspergillus fumigatus allergen	↓ IgE and ↑ IgG levels	–	S.C	Balb/c mice	Preparation with reverse micelles method	[111]
Copolymer of N-vinylpyrrolidone	OVA	↓ IgE and ↑ IgG levels	–	I.P or S.C	(CBAxC57BL/6) F1 , human	Self-assembly	[112]

(*continued on next page*)

Table 4 (*continued*)

Adjuvant	Cargo	Results		Administration route	Species	Comments	Ref.
		Immunologic parameters	Clinical parameters				
and maleic anhydride					leukocytes *in vitro*		
Gantrez®AN NPs	OVA and LPS	↑ IgG1, IgG2a and IL-10 levels	No anaphylaxis	Oral or I.D	Balb/c mice	Made from poly methyl vinyl ether-co-maleic anhydride	[113]
	lolium perenne and LPS	↑ IgG2a levels	No anaphylaxis	I.D	Balb/c mice		[114]
Polymethacrylic acid copolymer NPs	Ragweed	↓ IgE and ↑ IgG4 levels	↓ Medication and symptoms scores	Oral	Human clinical trial	–	[115]
	Timothy grass pollen	↓ T cell proliferation and IL-5 mRNA	↓ Medication and symptoms scores	Oral	Human clinical trial	–	[116]
Poloxamine nanosphere	Der f1 plasmid	↓ Inflammatory cytokines in BALF, ↑ TH1 responses	↓ AHR	I.M	Balb/c mice	Self-assembly and copolymers of ethylene oxide and propylene oxide	[117]
C(60) fullerenes	–	Blockade of cytoplasmic ROS levels	Inhibition of histamine release and anaphylaxis	–	Human mast cells and basophils *in vitro*, C57BL/6 mice	Carbon allotropes, negative regulator of allergic mediator release and a novel way to control Mast cell-dependent diseases	[118]
C(70)-tetraglycolate fullerenes	OVA	↓ IgE levels	↓ Airway inflammation, eosinophil and bronchoconstriction	I.N	C57BL/6 and Balb/c mice, human mast cells *in vitro*	Stimulates the production of an anti-inflammatory P-450 eicosanoid metabolites in the lung	[119]
C(60) fullerenes	OVA	↓ IgE levels, shift from TH2 to TH1, ↑ FoxP3 and filaggrin mRNA	No epidermal necrosis, destructive hemorrhage in dermis and hyperkeratosis	S.C or E.C	Balb/c mice	Strong antioxidant activity	[120]
Dextran-coated magnetic NPs	Bovine β-lacto globulin and ovomucoid	Increase allergen uptake by DCs	–	–	Human monocytes *in vitro*	Biocompatible	[121]
Aquasomes	–	↓ IgE and serum histamine levels, ↑ TH1 response	High survival rate, a lower decrease of the body temperature and prevention of anaphylactic reactions	I.D	Balb/c mice	Biocompatible, biodegradable, preparation by self-precipitation method	[122]
Thiamin-coated Gantrez®AN NP	OVA	↑ IgG2a and IgA levels	–	Oral	Balb/c mice	Bio-adhesive capacity	[123]
Polyanhydride NPs (coated with mannose or flagellin)	OVA	Balanced TH1 (IgG2a) and TH2 (IgG1) responses	–	Oral or S.C	Balb/c mice	Bio-adhesive capacity	[124]
Alginate-poly ethylenimine nanogels	OVA	↑ IFN-γ from TH1 and $CD8^+$ cells, ↑ IgG1 levels	–	LP	BMDCs from C57BL/6 mice	Bio-reducible and low toxicity, polymers with high porous, capacity of loading high volume of drug	[125]
Polypropylene sulfide (PPS) NPs	OVA	Enhancing IFN-γ secretion, ↑ cytotoxic and TH cell responses and DCs activation	–	–	BMDCs of C57Bl/6 mice	Macropinocytosis and clathrin-mediated endocytosis, biodegradable Pluronic -stabilized NPs, small size	[126]
Polypropylene sulfide (PPS) NPs	OVA and flagellin	Improving TH1 response	–	LN	C57BL/6 mice	–	[127]

Abbreviation: OVA, ovalbumin; **Ara h2**, *Arachis hypogaea*2; **Phl p 5b**, *Phleum pratense* 5b; **rFel d1**, recombinant major cat allergen; **Der p**, *Dermatophagoides pteronyssinus*; **Bet v1**, major allergens of birch**; I.M**, intramuscular; **I.P**, intraperitoneal; **I.N**, intranasal; **I.V**, intravenous; **S.C**, subcutaneous; **I.D**, intradermal; **E.C**, epicutaneous; **AHR**; airway hyperresponsiveness; **ROS**, reactive oxygen species.

Another approach targets oral APCs in a receptor-mediated manner due to the expression of several receptors such as FcγRII, FcγRIII, and FcεRI on oral APCs [71]. It has been observed that sublingual administration of allergens that bound to antibodies and targets. Fc-receptors decreased AHR and eosinophil infiltration and improved tolerance induction and showed anti-inflammatory activity in mice [72]. Thus, addressing the allergen through immunoglobulins could also be proposed for SLIT.

4. Future perspectives

Because of accessibility, noninvasive and immunological advantages, the oral mucosae, particularly the sublingual region, emerged as an attractive choice for allergen delivery during the past few years. Also, current understandings of oral immune system physiology and immune mechanisms underlie the induction of tolerance provide this opportunity to identify and develop novel allergen-presentation platforms to enhance the efficacy of SLIT for the future. Second-generation vaccines, specially adapted for the SLIT route, could be designated based on the molecular engineering power and innovative allergen delivery systems

[73].

So far, several TH1/Treg adjuvants and particulate delivery systems have been investigated in SLIT and frequently combined with natural allergen extracts. At the same time, it has been considered that platforms based on recombinant proteins will be a beneficial alternative to existing immunotherapies for developing efficient treatment routes in the future.

One hypothesis in this scope is the administration of formulations that could improve Allergen's presentation to oLCs, provoke allergen-specific regulatory T cells with a shift from TH2 toward TH1 favorable responses. In such formulations, mucoadhesive NPs and their potential for specific receptor bindings may increase the interaction between an allergen and oral mucosae, therefore facilitated Allergen capture by oLCs.

In Table 3 and Table 4, strategies have been proposed to simplify immunization and to enhance the tolerance induction for SLIT. So, in the future, SLIT can be designed based on these allergen-presentation strategies from previous clinical and animal studies in this era. Moreover, it is hoped that these adjuvants and carrier systems will be investigated for SLIT and resulted in safer and more efficient immunotherapy routes.

5. Conclusion

SLIT seems to be an appropriate approach in the treatment of allergic diseases. Identifying and using platforms for allergen presentation could augment sublingual allergy vaccines' efficacy and induce tolerance. So far, a variety of candidate adjuvants and delivery systems has been investigated in animal models and improved the SLIT efficacy, whether a few numbers of these formulations have been assessed in human researches. Therefore, clarify the benefits of these adjuvants demands further studies on SLIT in the years to come. Moreover, modulating or targeting desired immune cells and decreasing the allergen dose that leads to enhancing the profile of safety and efficacy are expected advantages of novel adjuvants and delivery systems. Also, many challenges are associated with the preparation of newly formulated allergens. Still, the accessibility of innovative allergen-presentation strategies allows for assessing a new generation vaccine in allergic patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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