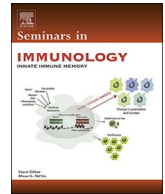




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Review

Differences and similarities between sublingual immunotherapy of allergy and oral tolerance

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ABSTRACT

Allergen immunotherapy is the only treatment altering the natural course of IgE-mediated allergies. Whereas the subcutaneous route for immunotherapy (SCIT) has been historically considered as a reference, we discuss herein the relative advantages of the sublingual and oral routes as alternatives to SCIT in order to elicit allergen-specific tolerance.

The buccal and gut immune systems are similarly organized to favor immune tolerance to antigens/allergens, due to the presence of tolerogenic dendritic cells and macrophages promoting the differentiation of CD4⁺ regulatory T cells. Sublingual immunotherapy (SLIT) is now established as a valid treatment option, with clinical efficacy demonstrated in allergic rhinoconjunctivitis (to either grass, tree, weed pollens or mite allergens) and encouraging results obtained in the management of mild/moderate allergic asthma. While still exploratory, oral immunotherapy (OIT) has shown promising results in the desensitization of patients with food allergies.

We review at both biological and clinical levels the perspectives currently pursued for those two mucosal routes.

1. Introduction

Immune tolerance is an important physiological process ensuring a state of non-responsiveness to self-antigens which involves the removal of autoreactive lymphocytes in the thymus as part of central tolerance mechanisms [1]. In addition, peripheral tolerance mechanisms control the response to non-harmful antigens (such as allergens), resulting into the deletion or anergy of inappropriately hyper-reactive T or B lymphocytes, or the induction of antigen-specific regulatory T cells [2].

Subsequently to the successful treatment of patients with hay fever in 1911 by Noon et al. [3], allergen-specific immunotherapy (AIT) has progressively emerged and remains as of today the only curative treatment for type I (IgE mediated) respiratory allergies (involving for example allergens from grass, tree or weed pollens, house dust mites or animal epithelia) as well as allergies to insect venoms [4]. Whereas AIT performed via the subcutaneous route (SCIT) has been considered historically as the reference, alternative routes have been sought in the 80's to circumvent some drawbacks associated with repeated subcutaneous injections of allergens, including a risk for severe systemic reactions and even infrequent fatal cases of anaphylaxis [5,6].

Sublingual and oral immunotherapies (SLIT and OIT, respectively)

are considered as two valid and distinct approaches to elicit oral tolerance to allergens, based on the credo that the induction of regulatory (suppressive) immune responses as opposed to effector (pro-inflammatory) responses, is a critical property of the immune system throughout the digestive tract which has selected during natural evolution [6–8]. Out of those two routes, only the sublingual one requiring maintenance of the allergen extract for a few minutes under the tongue prior to swallowing is currently established as a routine approach proposed to patients to elicit specific tolerance, whereas oral tolerance induction (*i.e.*, implying immediate swallowing of the allergen) remains exploratory as of today [9,10].

In relationship with these two routes, we review herein the similarities and specificities of the buccal and gut immune systems, as well as the strategies being currently explored to improve the efficacy of such mucosal allergy vaccines. We also discuss the clinical applications currently established or foreseen for SLIT and OIT as it applies to the prevention or the treatment of allergies.

Abbreviations: AIT, allergen immunotherapy; APC, antigen presenting cell; DBPC, double-blind placebo-controlled; DC, dendritic cell; IT, immunotherapy; LC, langerhans cell; MC, mast cell; MPL, monophosphoryl lipid A; OIT, oral immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TLR, toll like receptor

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2. Compared specificities of the buccal and gut immune systems

2.1. General immune mechanisms associated with allergen immunotherapy via mucosal routes

Irrespective of the route of administration, it is now broadly accepted that successful AIT redirects allergen-specific Th2 CD4⁺ cells (producing IL4, IL5 and IL13) towards a Th1 profile (IFN γ -secreting cells) [8,11]. In addition, AIT induces allergen-specific CD4⁺ regulatory T cells, including IL10-producing Tr1 and CD4⁺CD25⁺ cells. Reflecting those changes, evidence for an induction of regulatory dendritic cells (*i.e.*; DCs supporting the differentiation of regulatory T cells) with a downregulation of proallergic DC2s (supporting Th2-cell differentiation) was observed during successful AIT [12,13]. As a consequence of alterations in the cytokine milieu occurring following such changes in the polarization of allergen-specific CD4⁺ T cells and blood DCs, AIT further results in (i) a decrease of allergen-specific serum IgE antibodies together with an induction of IgG4s, the latter including potential high affinity “blocking” antibodies, and (ii) a downregulation of the recruitment and activation in target organs of pro-inflammatory cells such as mast cells, basophils and eosinophils [8,11,14].

Mechanistically, one advantage of mucosal routes over SCIT is that they elicit stronger allergen-specific local IgA responses, with the latter antibodies competing with IgEs for binding allergens directly at mucosal surfaces [8]. Also, systemic exposure to intact allergens is non-existent (for SLIT) or limited (for OIT) when compared to subcutaneous administration, thus reducing the risk for systemic side effects [8,15]. Also, as discussed in Subsections 2.2 and 2.3, the peculiar physiology of antigen presenting cells (APCs) throughout the digestive tract related to their bias in supporting the differentiation of regulatory T cells, likely explains why the default response is usually tolerogenic following sublingual or oral administration of the antigen/allergen [8,16].

2.2. Specificities of the buccal immune system: implications for sublingual immunotherapy

Biodistribution studies conducted in mice have confirmed that after administration under the tongue, allergens bind immediately to epithelial cells, likely through electrostatic interactions, prior to being captured within 15–30 min by DCs and macrophages as they penetrate and cross the mucosa [8]. Pharmacokinetics studies conducted in humans using the radiolabeled Der p 2 or Par j 1 mite or parietaria allergens, respectively, confirmed the immediate adhesion of significant amounts of allergens and the absence of a direct systemic absorption in the mouth, whereas the presence of the allergen (or derived peptides) can be detected in the blood after swallowing [17–19]. Importantly, due to such a rapid capture of the allergen following sublingual administration, the epitopic repertoire of the molecule is likely better preserved from proteolytic degradation in comparison with oral administration [8] (Fig. A1).

APCs identified so far in buccal tissues of mice and human consist of Langerhans cells (LCs), CD11b⁺CD11c[−] macrophage-like cells, conventional CD11b⁺CD11c⁺ DCs as well as plasmacytoid dendritic cells with a semi-mature phenotype (CD40[−]CD80[−]CD86⁺) [20–24] (Fig. A1). Those buccal APCs are located in distinct tissue compartments, *i.e.* the mucosa itself for LCs, the *lamina propria* for macrophages and conventional DCs and submucosal tissues for plasmacytoid cells. These cells can all play a role in tolerance induction during natural sublingual exposure of the antigen/allergen or SLIT, since to various degrees, they secrete IL10, TGF β and/or IL12. Both buccal LCs and macrophages express high affinity receptors for IgE (Fc ϵ RI), which likely facilitate the capture of allergens during SLIT [20,25,26]. Interestingly, cross-linking of Fc ϵ RI or stimulation of TLR4 receptors expressed on human buccal LCs induces the secretion of IL10, TGF β and the expression of indoleamine 2,3-dioxygenase (IDO) [27,28]. Buccal macrophages express RALDH1 and RALDH2 enzymes and as such, likely produce retinoic

acid, which is known to enhance TGF β -mediated induction of Foxp3⁺ in naïve CD4⁺ T cells [22,29]. In addition to those APCs, sublingual ductal epithelial cells were also recently shown to capture soluble antigens as well as antigens adsorbed on particles [30]. These epithelial cells could then transfer the antigen to buccal DCs or macrophages, possibly through exosomes or apoptotic bodies.

Given their above-mentioned characteristics, buccal APCs support the differentiation of naïve CD4⁺ T cells into IFN γ -secreting Th1 cells and/or IL10-producing Tr1 cells mediating a suppressive function against effector T cells [22,23,31]. In a murine model of peanut allergy, it was suggested that the repertoire of Tregs elicited by SLIT is mostly restricted to such Tr1 cells, in contrast to the broader range of regulatory T cells elicited during OIT (see Subsection 2.3) [32]. In humans however, SLIT regimens were shown to elicit not only Tr1 cells, but also both TGF β -secreting Tregs (likely Th3 cells) as well as Foxp3⁺CD4⁺CD25⁺ Tregs [31,33–36].

In mice and humans, resident mucosal CD4⁺ T cells encompass Th1, Th2 and Th17 subsets, which express the mucosal homing receptor CD103 and co-localize with CD11b⁺ tolerogenic APCs along the *lamina propria*, similarly to the organization found in the small intestine [21,37]. These resident T cells are likely involved in defense against infectious pathogens [38]. The human buccal immune system comprises in addition lymphoid tissues such as (i) the Waldeyer's ring associating the tonsils and adenoids as part of nasopharyngeal-associated lymphoreticular tissues, and (ii) cervical, submaxillary and jugular lymph nodes draining the buccal mucosae [8] (Fig. A1). Both the tonsils and the cervical lymph nodes represent lymphoid sites thought to foster regulatory T cell responses [8,39,40]. Tonsils also contain innate lymphoid cells, *i.e.* non-T, non-B lymphocytes which may contribute to both regulatory or effector innate immune responses [8]. Of note, pro-inflammatory cells, such as mast cells (MCs) and eosinophils, are present in buccal tissues, albeit in relatively low numbers [8,22,41]. Also, these cells are located in submucosal tissues.

2.3. Specificities of the gut immune system: implications for oral immunotherapy

The gastrointestinal tract is lined by a single layer of epithelium, directly in contact with antigens from the external environment present in the intestinal lumen. After swallowing, proteins are digested by gastric, pancreatic and small intestinal brush border proteases, and are thus progressively degraded as peptides and free amino acids, with only a small fraction of undigested proteins reaching the gut immune system (Fig. A1). This results in the destruction of numerous immunogenic epitopes, and thus to immunological ignorance to many proteins. Also, in contrast to the sublingual route, oral administration allows absorption of the allergens into the blood, mostly in the form of peptides, but nonetheless resulting in the possibility for some systemic exposure of IgE-reactive epitopes [17,19].

Similarly to the mouth, DCs and macrophages in the gut continuously capture, transport and present self-antigens as well as environmental proteins from mucosal tissues to lymphoid organs. In presence of TGF β and retinoic acid, all abundant in gut-associated lymphoid tissues, IL10-producing immature DCs as well as CD11b⁺CD11c⁺ DCs and CD163⁺ macrophages located in the *lamina propria* of the intestine elicit regulatory T cell responses [16,42] (Fig. A1). In the intestine, CD103⁺CD11c⁺ DCs located within the *lamina propria* can acquire the antigen through intestinal goblet cells delivering it from the intestinal lumen. Such CD103⁺CD11c⁺ DCs can migrate to mesenteric lymph nodes, and as such are likely critical to induce regulatory DCs during OIT [16,43,44]. CD163⁺ intestinal macrophages producing high constitutive levels of IL10 are also thought to contribute actively to oral tolerance [42,43]. A specificity of the gut immune system is that antigen sampling can occur at the level of Peyer's patches, *i.e.* organized lymphoid structures distributed in the small intestine and rectum, comprising a germinal center with IgA-producing B

lymphocytes surrounded by T lymphocytes [45,46]. Peyer's patches are overlaid by specialized epithelial cells, called microfold (M) cells, prone to capture particulate as opposed to soluble antigens and deliver them in the subepithelial dome region of the Peyer's patch (Fig. A1). Antigen capture by M cells is thought to lead to IgA-producing B cells and TGF β -secreting CD4⁺ T cells. Lastly, intestinal epithelial cells have also been reported to capture antigens in the lumen through fluid-phase endocytosis, and induce CD8⁺ suppressor T cells [45,46].

Regulatory T cells elicited during OIT are heterogeneous and include both TGF β -secreting Th3 cells expressing the latency-associated peptide (LAP), IL10-producing Tr1 cells and Foxp3⁺CD4⁺CD25⁺ cells [44,45,47–49] (Fig. A1). Such Tregs mediate a suppressive function, through either cytokine secretion or cell contact-dependent mechanisms involving the CTLA-4 or PD-1 molecules. Following antigen feeding using high doses, other tolerance mechanisms such as deletion of autoreactive T cells by apoptosis, or induction of anergy are also observed [1,45].

Although, as for the mouth, the gut immune system is clearly biased towards the induction of antigen/allergen specific tolerance, it also encompasses effector mechanisms involving for example resident mucosal CD4⁺ T cells belonging to Th1, Th2 or Th17 subsets [42,49]. Consequently, it retains the capacity to promote protective effector responses against infectious pathogens, either locally or in draining lymph nodes.

3. Clinical experience with sublingual immunotherapy

3.1. Safety and efficacy of SLIT in respiratory allergies

Allergen-specific SLIT has been investigated as an alternative to subcutaneous immunotherapy in patients with respiratory allergies since the mid-80's (Table A1). During SLIT, the allergen extract is applied as either a solution, a tablet or a loz (i.e., a solid form with immediate disintegration) and maintained under the tongue for 2–3 min, to allow allergen capture by buccal APCs. As of today, it is estimated that around two billion doses have been administered to humans. Classically, the allergens are subsequently swallowed, and it can thus be considered that SLIT efficacy is in part mediated by allergen exposure to the gut immune system. However, sublingual-spit protocols, used for example in patients exhibiting serious gastrointestinal side effects during sublingual-swallow procedures, are also clinically efficacious [50]. The latter observation confirms that allergen exposure to the buccal immune system leads to tolerance induction, even in the absence of gastrointestinal exposure.

SLIT is recommended by position papers from the World Allergy Organization (WAO) and the Allergic Rhinitis and its Impact on Asthma (ARIA) as a treatment for patients with allergic rhinoconjunctivitis, with or without mild-asthma, poorly controlled by pharmacological drugs [51,52]. The clinical efficacy of SLIT in treating type I respiratory allergies was initially documented by meta-analyses compiling results from multiple small scale clinical studies in patients allergic to seasonal (e.g., pollens from grass, birch, parietaria, ragweed, olive-tree, Japanese cedar) or perennial (house dust mites, cat dander) allergens [53–58]. It was definitely confirmed in the last decade in the context of numerous double-blind placebo-controlled (DBPC) phase III studies conducted in large cohorts of adults or children allergic to either grass, birch or ragweed pollens, or house dust mites, based on the evidence that it significantly reduces both rhinoconjunctivitis symptoms and the use of symptomatic medication [59–66]. Comparative clinical trials in birch pollen-allergic patients revealed no significant differences in terms of efficacy between SCIT and SLIT when high dose SLIT regimens were used [67]. SLIT was also shown to mediate a disease-modifying effect in patients allergic to grass pollen or house dust mites, with evidence for a sustained clinical benefit for up to two years after stopping treatment [63,68].

The safety profile of SLIT is very well documented in adults, but also

in 5–15 year old children, with evidence for mostly local reactions (in the form of oral pruritus, tongue swelling, lip oedema, throat irritation, ear pruritus) occurring in 40–75% of patients treated, classically at the beginning of immunotherapy and resolving spontaneously without any symptomatic treatment [69,70]. Systemic reactions are extremely rare during SLIT, likely as a consequence of the very limited exposure of intact allergens to blood immune cells, which constitutes a major advantage over SCIT [15]. The safety of high-dose sublingual immunotherapy has even been documented in children below 5 years of age, but whether SLIT can be routinely implemented in very young children remains to be further documented [71,72].

3.2. Perspectives for the sublingual route

3.2.1. Biological studies

There is as of today an interest in understanding pro-inflammatory mechanisms potentially elicited during buccal exposure to the allergen. For example, a strong inflammation of the mouth can be observed in patients allergic to food components cross-reactive with aeroallergens. A better understanding of the physiopathology of this so-called Oral Allergy Syndrome (OAS) is needed to avoid the recruitment of such pro-inflammatory mechanisms during SLIT [26].

Another area of active investigation is the characterization of the microbiota in the buccal cavity. An analysis conducted as part of the Human Microbiome Consortium identified strains belonging to the *Streptococcus*, *Haemophilus*, *Prevotella* and *Veillonella* species as the most prevalent commensal bacteria colonizing buccal tissues [73]. These studies have also provided evidence for significant differences between individuals in their buccal flora, although the implications of those differences in terms of health or disease, or response to SLIT are still unexplored as of today.

3.2.2. Second generation SLIT products

Although all sublingual vaccines commercially available are based on aqueous allergen extracts, some developments are being conducted relying upon recombinant allergens [74]. A recent phase II study has confirmed that SLIT with the r Bet v 1 major allergen from birch pollen is safe and efficacious in reducing rhinoconjunctivitis symptoms in birch pollen allergic patients [75]. On the basis of encouraging pre-clinical data obtained in murine asthma models, there is also a strong interest in considering adjuvants and vector systems to enhance tolerance induction to the allergens via the sublingual route [76,77]. For example, selected strains of *Lactobacilli* and *Bifidobacteriae*, as well as Toll like receptor 2 (TLR2) or TLR4 agonists, the B subunit of cholera toxin, or a combination of Dexamethasone with 1,25-dihydroxyvitamin D3 have all been shown to enhance SLIT efficacy in animal models [78–83]. Whereas all these adjuvants act as Treg, and for some of them also Th1 adjuvants, pure Th1 adjuvants do not potentiate tolerance induction via the sublingual route in such murine models [76]. In agreement with this observation, the TLR4 agonist monophosphoryl lipid A (MPL) had only a limited benefit in a SLIT trial in patients with grass pollen allergy, with a documented enhancement of specific IgG responses when using high doses of MPL [84].

Particulate formulations can also be considered to better target allergens to buccal APCs during SLIT [77]. In this regard, sublingual administration of the allergen formulated within mucoadhesive particles (made of either polysaccharidic, chitosan or maltodextrin polymers) enhances allergen-specific Th1 and Treg responses, while downregulating eosinophil infiltrates in bronchoalveolar lavages and specific Th2 responses in draining cervical lymph nodes [85–87]. The use of such vector systems to formulate the allergen enhances tolerance induction in mice with established asthma, leading to a dramatic reduction of both airway hyperresponsiveness and lung inflammation [85–87]. Although this concept of allergen vectorization has not been tested yet in humans, fusing the allergen to the adenylate cyclase (CyaA) from *Bordetella pertussis* to target CD11b⁺ buccal APCs has also

been shown to enhance dramatically SLIT efficacy in a murine asthma model [22].

3.2.3. New foreseen clinical applications

Several studies have been conducted to establish the value of SLIT in the treatment of allergic asthma, which represent today the next frontier for SLIT applications. Meta-analyses compiling such studies have concluded to the potential interest of SLIT in allergic asthma [54,88,89] and recent DBPC studies are confirming that SLIT is well tolerated and useful to control patients with mite-induced moderate, or even more severe asthma [90,91]. Limited evidence exists as well that SLIT with mite extracts decreases both the severity symptom score (SCORAD) and the use of symptomatic medication in patients with atopic dermatitis [92]. For these two clinical indications, additional large-scale studies are still needed to better document the safety and efficacy of SLIT.

More recently, SLIT has also been tested in small cohorts of patients with food allergies, for example to kiwi, cow's milk, hazelnut, peach and peanut allergens [93–98]. Results available so far suggest that SLIT is well tolerated, and allows some patients to tolerate higher cumulated doses of food allergens [96–98]. However, in a recent study evaluating the long term benefit of SLIT in patients allergic to peanut, only 11% of the patients achieved sustained unresponsiveness (*i.e.*, true tolerance) to the allergen after three years of treatment [99].

Lastly, given the excellent safety profile of SLIT, a pilot study has been initiated to prevent respiratory allergies using SLIT in 18–30 month-old children with a positive atopic family history. This study was inconclusive regarding the potential efficacy of SLIT in allergy prophylaxis and emphasized the difficulty to administer sublingual drops in this age group [100].

4. Clinical experience with oral immunotherapy

4.1. Safety and efficacy of OIT in respiratory and food allergies

Oral immunotherapy has been actively tested in patients with autoimmune diseases such as type I diabetes, multiple sclerosis, rheumatoid arthritis, uveitis or thyroiditis, using either antigenic peptides, or purified or recombinant proteins [1]. Unfortunately, whereas oral tolerance regimens have demonstrated promising results in experimental animal models of such autoimmune diseases, the latter were not confirmed in phase II/III trials in humans [1]. In the 80's, the efficacy of OIT was also assessed in both adult and pediatric patients with pollen-induced allergic rhinoconjunctivitis (Table A1) [101–104]. Several of these studies were performed with grass pollen allergens presented either as an aqueous solution, a powder or an encapsulated extract [102–104]. Although OIT was well-tolerated, it was poorly efficacious in alleviating the patients' symptoms, likely due to the use of low allergen doses. The latter was further corroborated by the lack of significant changes in serum allergen-specific IgG or IgE levels detected in comparison to placebo in those studies [105]. Interestingly, OIT relying upon either higher doses of aqueous allergen extracts from *Dermatophagoides pteronyssinus* or mugwort or Japanese cedar pollens [106–108], or encapsulated allergens from birch or ragweed pollens [109,110] proved to be more efficacious. High dose OIT also elicited a significant decrease in serum-specific IgE antibodies, together with the induction of IgG1/IgG4 antibodies.

Whereas as of today, OIT is not routinely used to treat respiratory allergies, it is actively investigated as a mean to reestablish the tolerance to dietary proteins in children with food allergies to cow's milk, egg proteins or nuts [94,111–116] (Table A1). In light of the risk of severe reactions, such OIT protocols commonly require the administration of incremental doses (from micrograms to milligrams to grams) of food allergens. The efficacy of OIT regimens is measured by determining before and after months to years of treatment with a maintenance dose the highest quantity tolerated by the patient during a food challenge. Several studies have confirmed that OIT with cow's milk, egg

proteins or peanut flour is successful in augmenting significantly (*e.g.*, by 10–100 fold) the tolerated dose of food allergen in 60–85% of patients [111,114,116]. In a majority of those patients however, short term desensitization to the food allergen is observed as opposed to true tolerance induction, in that the clinical benefit disappears when the treatment is stopped [117,118]. A limitation of many of those clinical studies is that they rely upon small cohorts of patients and often lack a control group to take into account the spontaneous outgrowth of the disease commonly observed in food allergic children.

In terms of biological changes, OIT for food allergies was shown to be associated with a significant decrease in the blood of food-specific IgE levels concomitantly with an increase in IgG4s, as well as a reorientation of preexisting Th2 responses towards regulatory T cells [119,120]. In this regard, both epigenetic changes at the *Foxp3*⁺ promoter locus, and exhaustion of Th2 cells have been noticed during successful OIT for peanut allergy [120,121]. Interestingly, some of those biological changes are also observed in children who are sensitized but tolerant, or who spontaneously outgrow their food allergy [122,123].

A residual drawback for OIT as it applies to food allergies is currently the severity of gastrointestinal side effects observed in approximately 25% of the patients. Also, due to systemic exposure of the allergen, OIT conducted with food allergens bears as well a risk of anaphylaxis [112,113].

4.2. Perspectives for oral immunotherapy

4.2.1. Biological mechanisms

Given the interest of the oral route to elicit antigen-specific tolerance, it is needed to better understand the pathophysiology of inflammatory conditions in which gastrointestinal tolerance is lost, such as for example celiac disease or inflammatory bowel diseases [45,46,49]. Such studies could shed light on immune mechanisms which should be recruited and others that should be avoided in the context of second generation OIT.

There is today a lot of interest as well in characterizing the commensal bacteria which colonize the gut, with the notion that microbiota in the intestine regulate the balance between regulatory T cells and Th1, Th2, Th17 effector responses, respectively [124,125]. Interestingly, metabolites, such as single chain fatty acids produced by selected commensal bacteria in the intestine have been shown to promote peripheral regulatory T cell generation [126,127]. As for SLIT, the Human Microbiome Project and related initiatives will shed further light on the existing polymorphisms in intestinal floras between individuals, as well as their potential impact on the patient's immune status and on the outcome of OIT [73].

4.2.2. Second generation OIT products

The comparative merit of using either food components, natural or hypoallergenic pharmaceutical-grade allergen extracts, recombinant allergens or allergen-derived peptides for OIT remains to be evaluated. As for sublingual vaccines, adjuvants and vector systems should be considered for the oral route. Such adjuvants include probiotics, with recent evidence that the combination of peanut flour with *Lactobacillus rhamnosus* may enhance OIT efficacy in peanut allergic children [128]. Vector systems are also relevant to induce allergen-specific tolerance in the context of OIT, as suggested by promising studies conducted with allergen formulations based on lectins and/or poly lactic-co-glycolic acid (PLGA) particles in murine models [129–132]. Also, to this aim, targeting the allergen onto tolerogenic DCs or macrophages in the gut using for example the non-toxic B subunit of the cholera or shiga toxins, the outer membrane protein A from *Klebsiella pneumoniae*, the bacterial cell surface protein of *Geobacillus stearothermophilus* (S-layer) or the anti DEC-2015 antibody could be considered [76,77]. As stated in Subsection 4.1, encapsulated pollen allergens have already been tested in humans with encouraging results [109].

4.2.3. New foreseen clinical applications

As of today, only a small number of trials have investigated whether OIT can lead to true tolerance, that is sustained non-responsiveness to food allergens after stopping treatment. Overall, these trials tend to suggest that a higher dose of allergens and a longer duration of OIT are better to promote sustained non-responsiveness and even tolerance [117].

Recently, comparative studies have been conducted to evaluate the relative efficacy of SLIT and OIT protocols in peanut allergic patients [133–135]. Overall, OIT protocols appear to be more efficacious, whereas SLIT regimens are safer. One advantage of OIT over SLIT is to allow administering higher doses of allergens (*i.e.*, gram versus milligram quantities) which may explain the superior efficacy of the former.

Oral tolerance is also being investigated as a mean to prevent allergy. In this regard, a prophylactic OIT study recently conducted using a daily administration for a year of a mite extract to infants less than one year of age with atopic heredity, but negative skin prick tests, showed only a reduction on subsequent sensitization to common allergens, but no effect on mite sensitization nor on prevention of eczema, wheeze and food allergy [136]. Other approaches to prophylactic oral tolerance are being investigated or considered in patients with a high risk of developing food allergies. For example, a large scale multiyear

study (LEAPs) documenting the benefit in atopic patients of a peanut-containing diet as opposed to allergen avoidance unambiguously concluded in favor of using the former for the prevention of peanut allergen sensitization [137]. Strategies to elicit oral tolerance in neonates following breast-feeding of the allergen are also being considered to prevent respiratory or food allergies [138].

5. Conclusions

The relevance of sublingual and oral immunotherapies as treatments for IgE-mediated allergies is supported by our recent understanding of the physiology of the buccal and gut immune systems. Specifically, both comprise various subsets of tolerogenic APCs biased to induce Treg responses capable to downregulate established allergen-specific Th2 responses. Based on considerable clinical experience accumulated in human, the sublingual route is as of today the only established mucosal route to induce allergen-specific tolerance in patients with respiratory allergies. OIT is however actively being tested in patients with food allergies, with promising results. Targeting the allergen to tolerogenic mucosal DCs using vector systems or adding adjuvant molecules represent a valid approach to further broaden clinical applications of tolerance induction via either one of those routes.

Appendix A

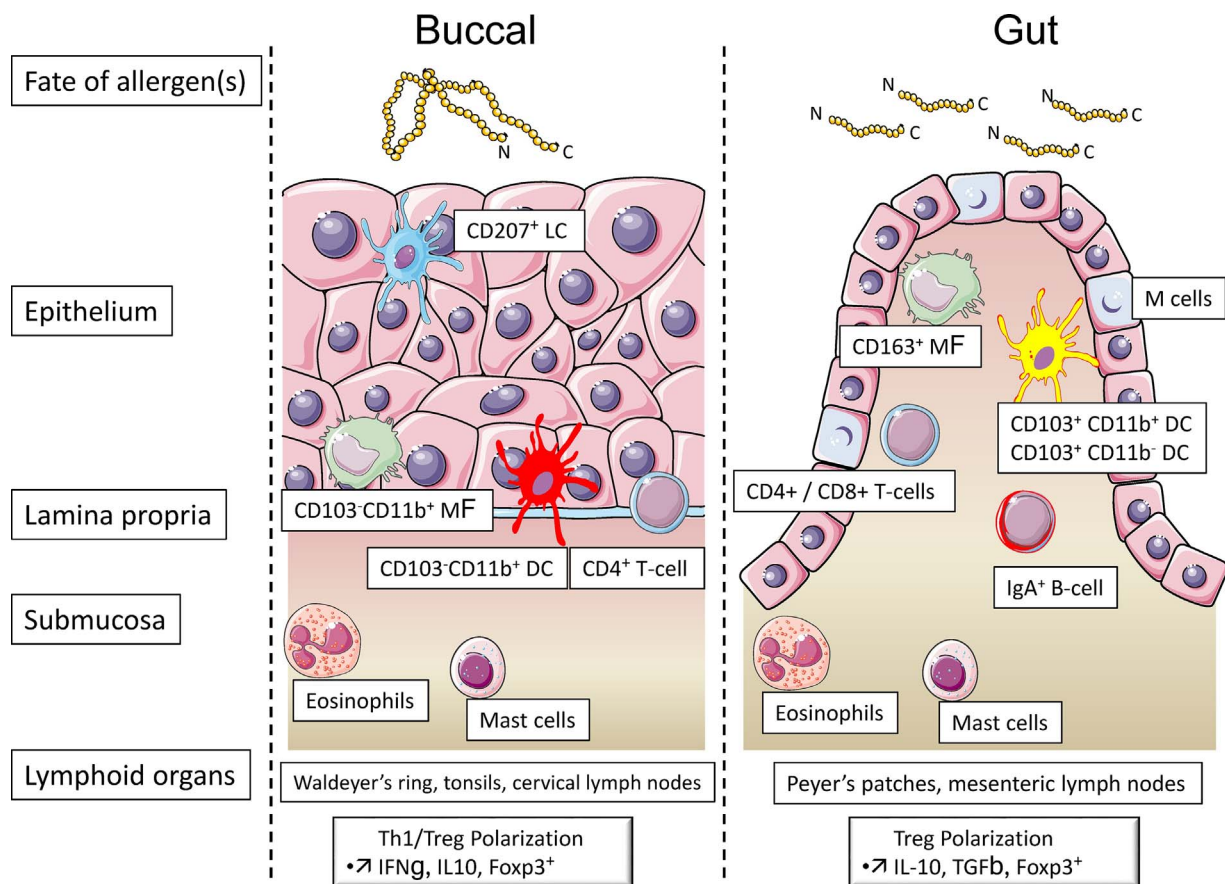


Fig. A1. Compared characteristics of the buccal and intestinal immune systems.

Left panel: Buccal APCs including CD207⁺ Langerhans cells, CD103⁺CD11b⁺ macrophages and CD103⁺CD11b⁺ DCs capture intact antigens/allergens and migrate to tonsils and lymph nodes where they induce naive CD4⁺ T cells to differentiate into IFN γ – secreting Th1 and IL10-producing regulatory T cells. Resident CD4⁺ T cells located along the lamina propria in the vicinity of APCs include Th1, Th2 and Th17 cells. Low numbers of pro-inflammatory cells (*i.e.* eosinophils and mast cells) are present in submucosal tissues.

Right panel: Gut APCs including microfold (M) cells, IL10-producing CD163⁺ macrophages, as well as CD103⁺CD11b⁺ and CD103⁺CD11b⁻ DCs capture the antigens/allergens mostly as peptides. These APCs then migrate to draining lymphoid tissues, including Peyer's patches and mesenteric lymph nodes, to elicit IL10 or TGF β -secreting Foxp3⁺ or Foxp3⁻ Tregs. IgA-producing B-cells as well as resident CD4⁺ and CD8⁺ T cells are present along the lamina propria. Mast cells are found in submucosal tissues, and only rare eosinophils are detected in the healthy intestine.

Table A1
Compared characteristics of sublingual and oral routes for allergen immunotherapy.

Routes	Allergens and formulations	Current status:	Refs.
Sublingual Immunotherapy (SLIT)	Natural aqueous allergen extracts from pollens (grasses, ragweed, birch, parietaria, olive tree, Japanese cedar), house dust mites, cat dander	- The buccal immune system is biased toward tolerance induction to the antigen/allergen due to the capacity of dendritic cells and macrophages to elicit strong Th1 and regulatory T cell responses. The antigen/allergen is presented to buccal APCs mostly as an intact molecule. - SLIT is efficient in treating type I respiratory allergies to either seasonal or perennial allergens. It reduces both symptoms and the need for symptomatic medication in adults and children. SLIT is recommended by international guidelines as a treatment for allergic rhinoconjunctivitis with or without mild asthma. - SLIT exhibits a disease modifying effect, with a long lasting effect for up to two years after stopping treatment.	[8,20–28,31–36]
	Formulated as drops, tablets, lyocs	- SLIT exhibits a very favorable safety profile, with moderate local side effects observed at the beginning of treatment in 40–75% patients. Systemic side effects are rare. - Perspectives for SLIT include the use of adjuvants and vector systems to formulate the allergen. New clinical applications are foreseen, such as the treatment of allergic asthma, atopic dermatitis and food allergies, as well as the prevention of respiratory allergies.	[4,10] [63,68] [15,69]
Oral Immunotherapy (OIT)	Natural aqueous allergen extracts from pollens (grasses, ragweed, mugwort, birch, Japanese cedar), house dust mites, food allergens (cow's milk, egg proteins, peanut flour)	- The gut immune system is biased toward tolerance induction to the antigen/allergen due to the capacity of dendritic cells and macrophages to elicit strong regulatory T cell responses. The antigen/allergen is presented to gut APCs mostly as peptides. - OIT using low doses of allergen is poorly effective in treating respiratory allergies. OIT with higher doses or encapsulated allergens has shown some efficacy in allergic rhinoconjunctivitis to respiratory allergens. - OIT is currently evaluated in children with food allergies to either cow's milk, egg proteins, peanut, with the aim to re-install tolerance towards these allergens. OIT for food allergies commonly results in allergen desensitization in a majority of patients (60–85%) and to a lesser extend tolerance induction. A limitation of this approach is the induction of significant gastrointestinal side effects, and a risk of anaphylaxis.	[42–48] [101–110]
	Formulated as solutions, powder forms, enterosoluble capsules	- Perspectives for OIT include the use of adjuvants (e.g., <i>Lactobacillus rhamnosus</i>) and vector systems, as well as the evaluation of protocols to prevent food allergy using oral tolerance.	[111–118,133–135] [77,129–132,136–138]

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