

Immunologic Aspects of Sublingual Immunotherapy in the Treatment of Allergy and Asthma

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Abstract: Recently interest has been focused on the administration of allergen specific immunotherapy by the oral route particularly sublingually. The mechanism by which sublingual immunotherapy exerts its effects remain unclear. Most likely, allergen captured within the oral mucosa by Langerhan's-like dendritic cells play a role in subsequent T cell responses. There is a growing body of evidence to support the role of regulatory T cells in controlling the development of allergic diseases. Nevertheless, there remains a lack of firm evidence that sublingual immunotherapy induces regulatory T cells. New vaccine developments with the increasing understanding of the molecular engineering techniques are on the way to offer the opportunity to design recombinant allergens that are safe, effective and easy to administer. In addition, the idea of using adjuvants along with allergen within the oral cavity is another promising approach.

Keywords: Adjuvant, allergy, asthma, oral dendritic cell, recombinant vaccine, sublingual immunotherapy.

INTRODUCTION

The impact of allergic disease in both developing and developed nations is considerable, forming a major source of discomfort for a large proportion of the population and a major healthcare expenditure. This phenomenon calls for the development of safe, effective and long-lasting therapies. Allergen specific immunotherapy (SIT) by the subcutaneous route has been shown to be an effective therapeutic tool for the treatment of respiratory allergic disorders [1], specifically restoring normal immunity against allergens and therefore offering a long-term solution. However, in early studies subcutaneous immunotherapy (SCIT) was associated with uncommon, but severe or even fatal systemic reactions [2]. As a consequence, the interest in alternative routes increased inspiring the search for non-injection routes of administration of allergen SIT. Therefore, delivery of allergens through mucosal route has been proposed, and it has been suggested that the natural mechanisms underlying the induction of oral tolerance at mucosal surfaces may be an effective therapeutic strategy for suppression of ongoing pathologic immune responses in allergic diseases [3]. The precise mechanisms by which oral tolerance is induced remain unclear, but it seems likely that the route of allergen processing and presentation is a critical determinant of the subsequent T cell response [4].

Previous studies evaluating the effectiveness and safety of specific immunotherapy by sublingual route in patients with rhinitis and asthma symptoms due to house-dust-mite (HDM) or pollen are encouraging [5,6]. Furthermore, the long lasting effect has been documented with a preventive effect on development and natural history of asthma [7,8]. On the other hand, in the systematic review and meta analysis of sublingual immunotherapy (SLIT) for allergic rhinitis, Wilson *et al.* concluded that this mode of immunotherapy is

not of particular benefit for allergic rhinitis in children [5]. Moreover, despite the use of SLIT in treatment of respiratory allergic disorders in clinical practice, our understanding of the underlying immunological mechanisms is limited. This review focuses on current data on immune mechanisms elicited during SLIT which provide a better understanding of this mode of therapy, and discusses the future developments.

MECHANISMS OF IMMUNOTHERAPY

Subcutaneous allergen SIT has been used most successfully in allergy to insect venoms, and in allergic rhinitis [9-11]. This mode of therapy has been shown to ameliorate allergen induced symptoms including i) antibody responses: upregulation of blocking antibody responses and downregulating allergen-specific IgE responses [12,13], T cell responses: reorientation of allergen-specific T-cell responses from T helper (Th) 2 to Th1 and/or regulatory T profile [14-16], iii) inflammatory cells: reduction in the numbers and activation of proinflammatory cells such as mast cells and eosinophils [17,18] (Fig. 1).

Hypotheses for the Mechanism of Action of SLIT

It seems likely that contact of the allergen within the oral mucosa may be critical for the success of SLIT [19]. What then makes the oral mucosa efficient in immunological processes leading to a reduction of allergic symptoms during SLIT? It is postulated that most likely Langerhan's-like local dendritic cells (DC) are involved in this process [20]. During SLIT, the allergen is most likely captured within the oral mucosa by Langerhan's-like DCs which may result in subsequent DC maturation and migration to proximal draining lymph nodes [21].

Antibody Responses

It has been suggested that the production of antigen-specific IgG antibodies can antagonize and "block" the allergic inflammation cascade resulting from antigen recognition by IgE. Therefore, the shift in balance between IgE and IgG4 is a phenomenon crucial for successful allergen-specific immunotherapy. While specific IgE levels did not change sig-

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nificantly after 70 days of SCIT for HDM, specific IgA, IgG1 and especially IgG4 increased significantly. This increase in specific IgA and IgG4 in serum coincides with increased TGF- β and IL-10 in allergen-specific peripheral blood mononuclear cell cultures [15].

On the other hand, the immunologic response to SLIT has not been intensely studied. A previous study reported changes in specific IgG4 levels [21], whereas others reported a lack of change in specific IgG4 [5] and IgE levels [22]. Moreover, in a recent study of HDM specific SLIT in asthmatic children, investigators reported a decrease in the IgE/IgG4 ratios where the downregulation of IgE in serum accompanied a slight upregulation of specific IgA, but with no effect on IgG1 and IgG4 [23]. Further studies are needed to clarify the role of blocking antibodies in SLIT.

T Cell Responses

Insight into healthy immune response to allergens has important implications for successful allergen-SIT [24]. Regulatory T cells represent the dominant allergen-specific subset in healthy individuals. In contrast, allergic individuals characteristically display a high frequency of Th2 cells specific for common environmental allergens. Regulatory T cells comprise predominantly of a constitutively expressed subtype of CD4(+)CD25(+) cells which are characterized by the expression of the transcription factor FoxP3, and an inducible subtype (Tr1) characterized by the secretion of IL-10 and TGF- β . In humans, circumstantial evidence suggests that a major role is played by both types of T regulatory cells in the inhibition of allergic disorders [25]. Another type of regulatory cell, T helper type 3 (Th3) produces IL-4, TGF- β and IL-10 and are induced following oral administration of the antigen [21].

Regulatory T cells can control an established allergic response through distinct mechanisms including T cell tolerance which can be directly initiated by the autocrine action of IL-10 and TGF- β [15,16]. IL-10 is a potent suppressor of both total and allergen-specific IgE, while it simultaneously increases IgG4 production [16]. Meanwhile, TGF- β induces IgA production [26]. This may account for the role of IgA and TGF- β , as well as, IgG4 and IL-10, in peripheral mucosal immune responses to allergens in healthy individuals. As noted before, this balance between IgE, IgG (particularly IgG4) and IgA is a crucial factor in determining the successful outcome of allergen SIT.

According to animal models of atopy mucosal vaccination with allergens has addressed this route as a potential candidate for mucosal tolerance induction. In a murine model of birch pollen allergy, intranasal application of Bet v 1 suppressed IgE-dependent basophil degranulation, specific IgG1 and IgG2a titers, as well as, IL-5 production *in vitro*. In addition, RT-PCR analyses of splenocytes revealed that tolerance induction was associated with enhanced expansion of TGF- β , IL-10 and Foxp3 mRNA in CD4(+) T cells [27].

Yet, there is still no firm proof that SLIT is able to induce regulatory T cells in clinical practice. Nevertheless, a recent preliminary study showed that compared with untreated controls, SLIT increased IL-10 production in peripheral blood mononuclear cells from patients with HDM allergy, following *in vitro* stimulation with *Dermatophagoides* antigens, as

well

as, recall antigens such as *Candida albicans* or phytohemagglutinin [21]. In another study in childhood asthma with HDM allergy, 6 and 12 month of SLIT downregulated specific IgE response, while slightly increased specific IgA [23]. This suggests that further investigations are warranted to study the role of T regulatory cells, IL-10 and TGF- β in allergic subjects treated with SLIT.

Oral-Mucosal Immune Responses

In order to provide experimental basis for understanding the relationship between route of administration and mechanisms of action, allergen labelled with Iodine-123 has been used for pharmacokinetic studies [28]. In subjects receiving the radiolabelled allergen orally plasma radioactivity rapidly increased peaking at about 30 minutes, while in those given sublingually plasma radioactivity was not detectable until swallowing. Moreover, a relevant amount of Iodine-123 labelled allergen persisted in the sublingual region for up to 40 hours after administration.

It is postulated that most likely Langerhan's-like local DCs are critically involved in this process [20]. The difference between oral Langerhan's cells and their skin counterparts may be suggested to play role in the induction of immunological responses to SLIT. Oral Langerhan's cells exhibit constitutive high expression of the Fc portion of IgE (Fc ϵ receptor type I or Fc ϵ RI), major histocompatibility complex (MHC) class I and II, as well as, co-stimulatory molecules (CD40, CD80/B7.1, CD86/B7.2) which may implicate the role of these cells within the regional immune system of the oral mucosa [29]. The Fc ϵ RI-bearing DCs in oral mucosa might bind allergen-specific IgE *via* Fc ϵ RI and thereby, play a role in the uptake and presentation of allergens.

In a recent study, nasal and oral mucosal CD1a(+) myeloid DCs of atopic and non-atopic individuals were studied and compared. Both nasal and oral DC types shared the feature of Fc ϵ RI expression, but differed in (i) surface density of Fc ϵ RI, (ii) lineage specificity, (iii) myeloid marker, and (iv) costimulatory and MHC class expression. Furthermore, this study found that the lipopolysaccharide (LPS) receptor CD14, present on both nasal and oral myeloid DCs, was at higher density in oral DCs [20]. Moreover, in this study the Langerhan's cell-associated lectin CD207 was expressed both by oral and nasal DC types, but mostly on oral DCs. This resulted in a conclusion that oral DCs represent a more homogenous DC population [20].

FUTURE DEVELOPMENTS

While safety and efficacy of allergen-specific SLIT have now been largely documented and significant process has been made in the understanding of specific mechanisms underlying oral immunity and mucosal tolerance, we are still confronted with several new issues that are on the way to be addressed in the near future:

- What is the optimal concentration and regimen to induce mucosal tolerance by SLIT?
- Is the use of genetically engineered allergens meaningful for SLIT?

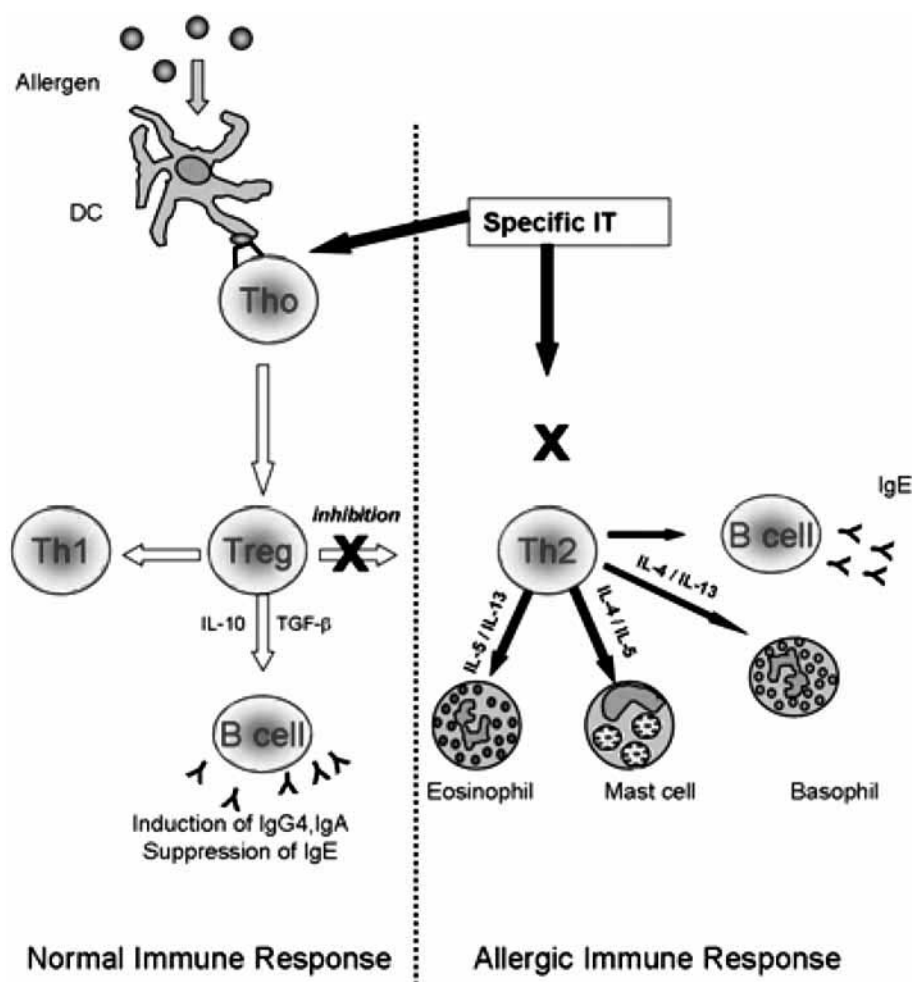


Fig. (1). Normally allergens captured by dendritic cells (DC) are presented to naive T cells (Th0). In a normal immune response T regulatory cells induce blocking antibody production through B cells, mostly IgG4 and IgA class, whereas they suppress IgE production. On the other hand, in an allergic individual Th2 type cells and their cytokines IL-4, IL-5, IL-13 act on eosinophils, mast cells and basophils, as well as on B cells which results in IgE isotype switching. According to the current understanding of the immune mechanisms underlying allergen-SIT, stimulation of DCs through IgE dependent epitopes may directly elicit an allergen-specific Th1 or regulatory T cell response, thereby down-regulating allergen specific IgE responses and inflammatory cells responsible for allergic symptoms.

- Can the use of adjuvants be effective in SLIT?

Dose and Regimen of SLIT

Although results of previous clinical studies suggested that reaching a threshold cumulative dose is important for clinical efficacy, it is speculated that current vaccines may not target oral mucosal immune cells but only with high dose regimens sufficient amount of allergen is captured by oral mucosal DCs. Exposure to high doses of allergen during IT may promote the skew of allergen-specific T cell response from Th2 to Th1 pattern in atopic patients. On the other hand, the influence of allergen dosage on regulatory T cells is not well established. Higher doses of allergen administration may promote proliferation and activation of regulatory T cells leading to establishment of T-cell mediated memory and induction of tolerance. Therefore, development of future SLIT vaccines should take into account both results of controlled clinical studies with high dose regimens and experimental data on underlying immunological mechanisms.

Up to date in almost all clinical studies allergen-specific SLIT had been administered in the form of drops. Change to tablet formulation could provide an advantage by increasing stability, compliance and ensure standardization of doses [30]. Moreover, in recent studies sublingually administered grass allergen tablets in high doses have been demonstrated to be clinically efficient with a good safety profile in asthmatic patients with rhinoconjunctivitis [31-33]. Experimental studies evaluating the underlying immune mechanism of those high-dose tablet regimens are warranted.

Recombinant Sublingual Allergen Vaccines

The current understanding of the immune mechanisms underlying allergen-specific immune responses, as well as, the power of molecular engineering and innovative antigen delivery systems offers the opportunity to design recombinant vaccines specifically tailored for the sublingual route. Recombinant allergens have several advantages over crude extracts. They are molecularly defined and are therefore easier and more reproducible and traceable to produce, and, can

easily be modified to create truncated or fusion proteins [34-36].

The best approach for immunization by the sublingual route may be to rely on recombinant allergens presented in their most native conformation, which would allow maximal IgE-mediated targeting and capture of allergens by the Fc portion of IgE on DCs in the oral mucosa [34,37]. This stimulation of oral DCs through IgE-dependent epitopes may directly elicit an allergen-specific Th1 or regulatory T-cell response [36]. This is probably unique to the oral route of allergen administration, as oral-mucosal DCs are known to express constitutively both high (FcεRI) and low affinity (CD23) receptors for IgE [20]. With this in mind, it is suggested that IgE binding to allergens produced in native conformation may facilitate capture by these oral DCs, followed by the production of IL-10 and TGF-β and thereby, upregulation of indoleamine deoxygenase; which suggests that native recombinant allergens have the potential to provide appropriate signals for the induction of allergen-specific regulatory T cells [21,34].

To date, several hundred allergens have been cloned and expressed as recombinant proteins. In this approach, the allergen cDNA is inserted into a heterologous expression host system (e.g. bacterium, yeast, mammalian or plant) to produce highly purified proteins [33-35,38,39]. In a number of studies recombinant allergen vaccines based on wild-type or modified forms of birch, Bet v 1 and combination of five timothy grass pollen allergens have been used by the subcutaneous route with promising results [35,36,39,40]. To date no sublingual recombinant allergen vaccine has been yet tested in humans.

Adjuvants

Other allergen-specific immunotherapy vaccine preparation strategies should perhaps consider the use of allergen in conjunction with an adjuvant within the oral cavity, which may further potentiate the immunomodulatory effect of SLIT towards protection from allergy [42,43]. This approach would help to reduce allergen dosage and simplify immunization regimens. Regulatory T-cell adjuvants specifically potentiating allergen presentation to oral DCs might be useful in this regard [43].

Furthermore, recently Allam *et al.* demonstrated that oral mucosal DCs express higher amounts of LPS receptor CD14 when compared to other types of DCs [20]. LPS, like other potential bacterial adjuvants such as *Mycobacterium vaccae* and *Lactobacillus plantarum* have the potential to redirect Th2-type immune responses towards Th1 and/or T regulatory type [44-49]. This might be important in the selection of potential adjuvants for oral-mucosal immunotherapy.

In view of the resistant flora within the oral cavity, it is tempting to speculate that microbial products or other biologic adjuvants may be used to trigger the production of IL-10 and/or TGF-β by antigen presenting cells, while enhancing migration to local lymph nodes to ensure T-cell priming, and thereby skewing of T-cell responses towards regulatory T cells by the engagement of surface particular receptors such as Toll-like receptors [21,49,50].

CONCLUSION

Despite the use of SLIT in the treatment of respiratory allergic disorders, our understanding of the underlying immune mechanisms remains to be elucidated. Over the last years advances have been made in the understanding of tolerance induction against allergens by mucosal vaccines. In addition the power of molecular engineering and innovative antigen delivery systems offer the opportunity to design rational second generation recombinant vaccines specifically tailored for the sublingual route. Moreover, the use of immunomodulatory and antigen-directing adjuvants together with oral mucosal allergen vaccination may further potentiate the immunogenicity towards allergy protection and tolerance induction.

ABBREVIATIONS

DBPC	=	Double-blind placebo-controlled
DC	=	Dendritic cell
HDM	=	House dust mite
LPS	=	Lipopolysaccharide
MHC	=	Major histocompatibility
SCIT	=	Subcutaneous immunotherapy
SIT	=	Specific Immunotherapy
SLIT	=	Sublingual immunotherapy
Th	=	T helper

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