SUBLINGUAL IMMUNOTHERAPY: What is the role in mucosal tolerance induction?

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Delivery of allergens through mucosal route has been proposed to initiate the natural mechanisms underlying the induction of oral tolerance at mucosal surfaces. It may be an effective therapeutic strategy for suppression of ongoing pathologic immune responses in allergic diseases [1]. The precise mechanisms by which oral –mucosal 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 [2].

It seems likely that contact of the allergen within the oral mucosa may be critical for the success of sublingual immunotherapy (SLIT) [3]. 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 [4]. 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 [5].

Systemic Immune Response to SLIT

A previous study reported changes in specific IgG4 levels [5], whereas others reported a lack of change in specific IgG4 [6] and IgE levels [7]. 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 [8]. Further studies are needed to clarify the role of blocking antibodies in SLIT.
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 [9,10]. IL-10 is a potent suppressor of both total and allergen-specific IgE, while it simultaneously increases IgG4 production [10]. Meanwhile, TGF-β induces IgA production [11]. 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. This balance between IgE, IgG (particularly IgG4) and IgA is a crucial factor in determining the successful outcome of allergen specific immunotherapy.

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 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 [12]. 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 phytohemaglutinin [5]. In another recent study in children with allergic rhinoconjunctivitis undergoing pollen SLIT, Valovirta E. et al demonstrated an upregulation of IL-10 mRNA and downregulation of IL-5 increase. In addition, TGF-β mRNA expression in PBMC was positively correlated with IL-10, and negatively with IL-5 increase [13]. 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 (Figure 1) [14].

**Oral-Mucosal Immune Response to SLIT**

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 receptor type I or Fc 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 [15]. The FcεRI-bearing DCs in oral mucosa might bind allergen-specific IgE via Fc 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 FcεRI expression, but differed in (i) surface density of FcεRI, (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 [4]. 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 [4].

**Promising Advances of SLIT**

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. 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 [16,17]. This stimulation of oral DCs through IgE-dependent epitopes may directly elicit an allergen-specific Th1 or regulatory T-cell response [18]. 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 [4]. 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 [5,16].
Concluding remarks

Current understanding of the immunological mechanisms underlying allergen-specific immunotherapy, particularly the role of T regulatory cells in allergen-specific peripheral tolerance, may enable novel treatment strategies. Application of recent advances in understanding of this area may result in more rational and safer approaches that, in the future could result in the prevention and cure of allergic diseases.
References:


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Figure 1. Peripheral tolerance mechanisms in allergen specific immunotherapy and healthy individuals

Immune deviation towards T regulatory cell response is an essential step in allergen-specific immunotherapy. T regulatory cells secrete IL-10 and TGF-β, which induce IgG4 and IgA production in...
B-cells. These two cytokines directly or indirectly suppress the effector cells of allergic inflammation. In addition, T regulatory cells may down-regulate cytokine production in Th2 cells, thus suppressing IgE production.