

## Pathophysiological Mechanisms Underlying the Efficacy and Safety of Sublingual Immunotherapy

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### Abstract

The results of meta-analyses show that sublingual immunotherapy (SLIT) is as efficacious as subcutaneous immunotherapy (SCIT) and more safe in treating patients with allergic rhinitis. In both issues, immunity of the oral mucosa, that is more oriented to tolerance to antigens than respiratory mucosa or skin, plays a pivotal role. In particular, the immunological organs contained in the Waldeyer ring, that is, adenoids, tubal tonsil, palatine tonsil and lingual tonsil are currently investigated concerning their specific function in the response to the allergens administered by SLIT. These studies have the prospective to improve the understanding of immunity of the oral mucosa and to refine the techniques to deliver SLIT.

**Keywords:** Sublingual immunotherapy; Efficacy; Safety; Immunity of the oral mucosa; Waldeyer ring

### Editorial

Sublingual immunotherapy (SLIT) is an efficacious treatment of allergic rhinitis, as clearly demonstrated by meta-analyses [1-3], based on its capacity to work on the causes of allergy and not only on symptoms, as drugs make instead [4,5]. This outcome is related to the mechanisms of action of allergen immunotherapy, that appear to be similar for SLIT and the traditional, subcutaneous immunotherapy (SCIT) and mainly consist in the generation of T regulatory cells favoring tolerance to the administered allergens and the shifting from the Th2 cytokine profile (typical of allergy) to the Th1 profile [6]. However, some diversities are apparent between the two routes of administration, that are likely to be due to the different pathophysiology of the skin and the oral mucosa. For example, the safety of SLIT is better than SCIT, the most common reactions occurring locally in the mouth, while systemic reactions are rare and anaphylactic reactions extremely rare [7,8]. Such good safety profile allows to administer by the sublingual route allergen doses much higher (up to hundreds of times) than those injected by SCIT. Also, the high safety of SLIT permitted to perform the treatment in patients allergic to house dust mites by a schedule alternating two months of SLIT and two months of interruption, with re-start of the treatment without repeating the build-up phase [9]. Of course, such schedule is not feasible for SCIT, because of the risk of systemic reactions.

The background for this kind of approach is provided by studies investigating the pathophysiology of the oral mucosa. A cell type particularly involved in allergic reaction is the mast cell, due to its capacity to rapidly release mediators such as histamine and leukotrienes as well as inflammatory cytokines [10]. In a study assessing by biopsies the cellular changes occurring in local oral reactions to SLIT, a low number of mast cells was found in subepidermal level in perivascular sites, some with surface IgE, with no significant differences in biopsies before and after the administration

of the allergen extract [11]. This suggests that events other than mediators release by mast cells are involved in local reactions to SLIT. As far as the mechanisms underlying the efficacy of SLIT are concerned, in recent years the role of the set of immunological organs defined as Waldeyer ring, that has the function of producing antibodies toward the common environmental antigens and includes adenoids, tubal tonsil, palatine tonsil, and lingual tonsil, was also investigated. Palomares et al. suggested that human tonsils may be potential first-line organs of oral tolerance induction by producing allergen-specific FOXP3<sup>+</sup> Treg cells [12]. Focusing the interest on SLIT, it has been reported that performing a polymerase chain reaction (PCR) array on mRNA extracted in adenoid samples from allergic children treated by SLIT, a reduced expression of IL-4, CCR2, CCR3, and PTGDR2 (Th2 related genes) and CD28, IL-2, and INHA (Th1 related genes) was found [13]. Ongoing studies are investigating the particular role of lingual tonsil. In bovines, immunohistochemical analysis suggested that the lingual tonsil can be considered as an inductive site, sampling and processing antigens to stimulate naïve T and B lymphocytes. Since this tonsil can be located macroscopically by the openings of its follicular crypts at the root of tongue, its localization in bovines was described as a prerequisite for the removal of specified risk material from the tongue meat to prevent the risk of bovine spongiform encephalopathy [14]. Concerning humans, preliminary findings indicate that materials sublingually administered to sensitized subjects, containing the specific allergen or inert substances, are rapidly driven to the lingual tonsil, that is apparently an initial sampling site from where the different destination of antigens is programmed [15].

Indeed, the disposition of the immunological organs in the oral mucosa to favour tolerance is easily understandable if one considers that all foods pass through the mouth and the occurrence in the oral mucosa of the same defensive attitude of the immunological organs in the respiratory tracts or in the skin would make feeding impossible. However, the specific role of the single components of the Waldeyer ring is far from clear. The current research line on this issue could pave the way to studies aimed at improving the understanding of immunity

of the oral mucosa and refining the administration techniques to perform SLIT.

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