

LETTER TO THE EDITOR

IS LINGUAL TONSIL A PREFERENTIAL TARGET FOR PROCESSING SUBLINGUALLY ADMINISTERED MATERIALS?

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The oral cavity is a site of pivotal importance in the immune response to foreign antigens, ensuring tolerance induction to harmless agents but reactivity to potentially noxious antigens. Tolerance or reactivity are driven by a number of secondary lymphoid organs, all belonging to the Waldeyer ring, that include adenoids, tubal, palatine and lingual tonsils. Waldeyer's ring tissues were acknowledged as implicated not only in the adaptive immune system but also in the innate immune system modulation, involving the toll-like receptors. In particular, findings from animal studies suggested that the lingual tonsil can be considered as an inductive site sampling and processing antigens to stimulate naïve T and B lymphocytes. According to a recent study showing that immunologically active or inactive materials placed under the tongue of allergic subjects rapidly reach the lingual tonsil, such a role seems likely also in humans, and warrants to be investigated in-depth for possible applications in medical treatments.

To the Editor,

The oral cavity is an anatomical site of critical importance for the development and persistence of the immune response, where both immune tolerance and immune reactivity can occur (1). Immune tolerance induction, however, generally prevails over reactivity to maintain immune homeostasis. This silencing immune function of the oral cavity is particularly crucial in view of the high level of exposure of the oral mucosa to the countless foreign antigens, e.g. commensal microbes, food proteins, that contact the body through this natural portal of entry. In the oral cavity there is a high density of secondary lymphoid organs (2) that play a crucial role in several immune functions and include tissues such as adenoids, tubal, palatine and lingual tonsils, all belonging to the Waldeyer ring, a structure that was described

in the 19th century (3). Within these tissues, antigen uptake is mediated by the M cells, that represent a specialized subset of mucosal epithelial cells that transport antigens across the mucosal barrier by transcytosis and are also involved in processing and presentation of antigen to T cells, directing the immune response towards either tolerance or immune reactivity (4). It is now acknowledged that Waldeyer's ring tissues are implicated not only in the adaptive immune system but also in the innate immune system modulation, involving the toll-like receptors, a family of innate pattern recognition receptors producing pro-inflammatory cytokines and chemokines (5). As far as the role of T cells is concerned, a reduced expression of IL-4, CCR2, CCR3, and PTGDR2 (Th2 related genes) and CD28, IL-2, and INHA (Th1 related genes) was reported by using an mRNA technique on adenoidal

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tissues of allergic children treated with sublingual immunotherapy (6). Recent studies examining the role of tonsils as a first-line immunological organ highlighted the importance of dendritic cells and T cells contained within these structures (7-9). For example, allergen-specific CD4(+)FOXP3(+) Treg cells were identified both in lingual and in palatine tonsils, with much higher levels when compared to peripheral blood, and their reduction in atopic vs non-atopic people was related to an allergen-specific response (8). However, from embryological studies on the lymphatic system, it is known that the palatine tonsils are derived from the second pair of pharyngeal pouches, while the lingual tonsils develop from aggregations of lymph nodules in the root of the tongue (10), thus suggesting a possible different immunological role of the two lymphoid organs.

Of interest, immunohistochemical studies performed in bovines suggested that particularly the lingual tonsil can be considered as an inductive site sampling and processing antigens to stimulate naïve T and B lymphocytes (11). According to a recent report, such role could be exerted also in humans. In fact, it was shown that a material placed under the human tongue, regardless its inactive or active nature, rapidly reaches the lingual tonsil. This data suggests a pathophysiologic importance (12) that deserves to be investigated in-depth and may have, if confirmed, relevant consequences in improving, by facilitating the contact with the lingual tonsil, medical treatments such as vaccinations or any other therapy aimed at influencing the immune response.

DISCLOSURE: C. Incorvaia is a scientific consultant for Stallergenes Italy. The other authors declare they have no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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