

NEWS & VIEWS**Groundbreaking Discoveries in Clinical & Basic Science**

Word of mouth: Oral mucosa composition in health and immune disease

Oral mucosa is composed of a multilayered squamous cell epithelium that acts as a barrier that is constantly exposed to external threats, such as allergens, pathogens or mastication forces. There are structural differences in oral mucosa: while lining (buccal) mucosa is composed of lightly keratinized epithelium, masticatory mucosa (gingiva) is highly keratinized. There are also other areas of specialized tissue like the dorsal tongue, which has taste buds.¹

Oral gingiva is commonly affected by periodontitis, a highly prevalent inflammatory disease that affects ~10% of the general population. It is caused by dysbiosis of the oral microbiome that triggers aberrant immune activation.

Recently, Williams et al² have investigated the composition, function and crosstalk between the stromal and immune cells in healthy oral mucosa and gingival mucosa suffering from periodontitis. They performed single-cell RNA sequencing and validated their results by histology and flow cytometry. They found that, compared with other mucosal tissues, gingival mucosa had a unique expression of neutrophil-related genes in the epithelial compartment, while buccal mucosa had increased endothelium development. Moreover, they observed that periodontitis induced inflammatory cell infiltration (neutrophils and IgG⁺ plasma cells) and a shift in the epithelial and stromal compartments towards a pro-inflammatory environment, marked by increased immune cell adhesion and chemokine secretion. Fibroblasts and epithelial cells specifically promoted neutrophil recruitment via cytokine biosynthesis (IL-8), and fibroblasts also expressed several neutrophil-recruiting chemokine ligands (CXCL1, 2, 5, 8) in periodontitis, thus suggesting a role of stromal cells in the establishment of the pro-inflammatory environment (Figure 1).

These results go in line with what has been observed in respiratory allergic diseases. It is widely accepted that the oral mucosa presents a unique pro-tolerogenic environment. However, a systemic Th2 response has been shown to impair oral tolerance by

shifting the phenotype of Tregs towards a Th2-like phenotype in animal models,³ thus promoting allergy. The mechanisms behind the loss of oral tolerance are not completely understood, but the impairment of the oral mucosal barrier might play a pivotal role on it.⁴ Interestingly, the epithelial disruption observed in the oral mucosa of patients suffering from respiratory allergies with no associated food allergy was not associated with an increase in the infiltration of immune cells.⁴ However, there is a lack of knowledge regarding the mechanisms behind this change of phenotype or how that could affect the oral mucosa in the long term. One possibility could be the affectation of basal cells. It has been shown that extensive local Th2 activity is able to block productive basal cell differentiation in chronic allergic rhinitis and other pathologies even after the Th2 environment is removed, promoting the barrier disruption.⁵

In celiac disease (CD), oral mucosa has been shown to have an increased abundance of Treg cells that was inversely correlated with E-cadherin expression and positively correlated with peripheral amphiregulin expression. Thus, we hypothesize that the Treg cells observed in CD patients are recruited to protect against further tissue damage and maintain barrier integrity.⁶

These publications advance the knowledge of the immune system of the oral mucosa in health and disease. The role of neutrophils seems to not be significant in the buccal mucosa for other inflammatory diseases, although this might be due to the location of the tissue (gingiva vs buccal mucosa).^{2,4,6} In this regard, oral mucosa is affected in periodontal, allergic and celiac disease, among others; thus, a full characterization of neutrophil, Th2 and Treg response in the oral mucosa could serve as a powerful, accessible tool to understand local and systemic disease. Moreover, other cell populations, such as innate lymphoid cells, and the function of the many antigen-presenting cells of the human oral mucosa should be further investigated to understand their role when oral tolerance is lost.

Abbreviations: Tregs, regulatory T cells.

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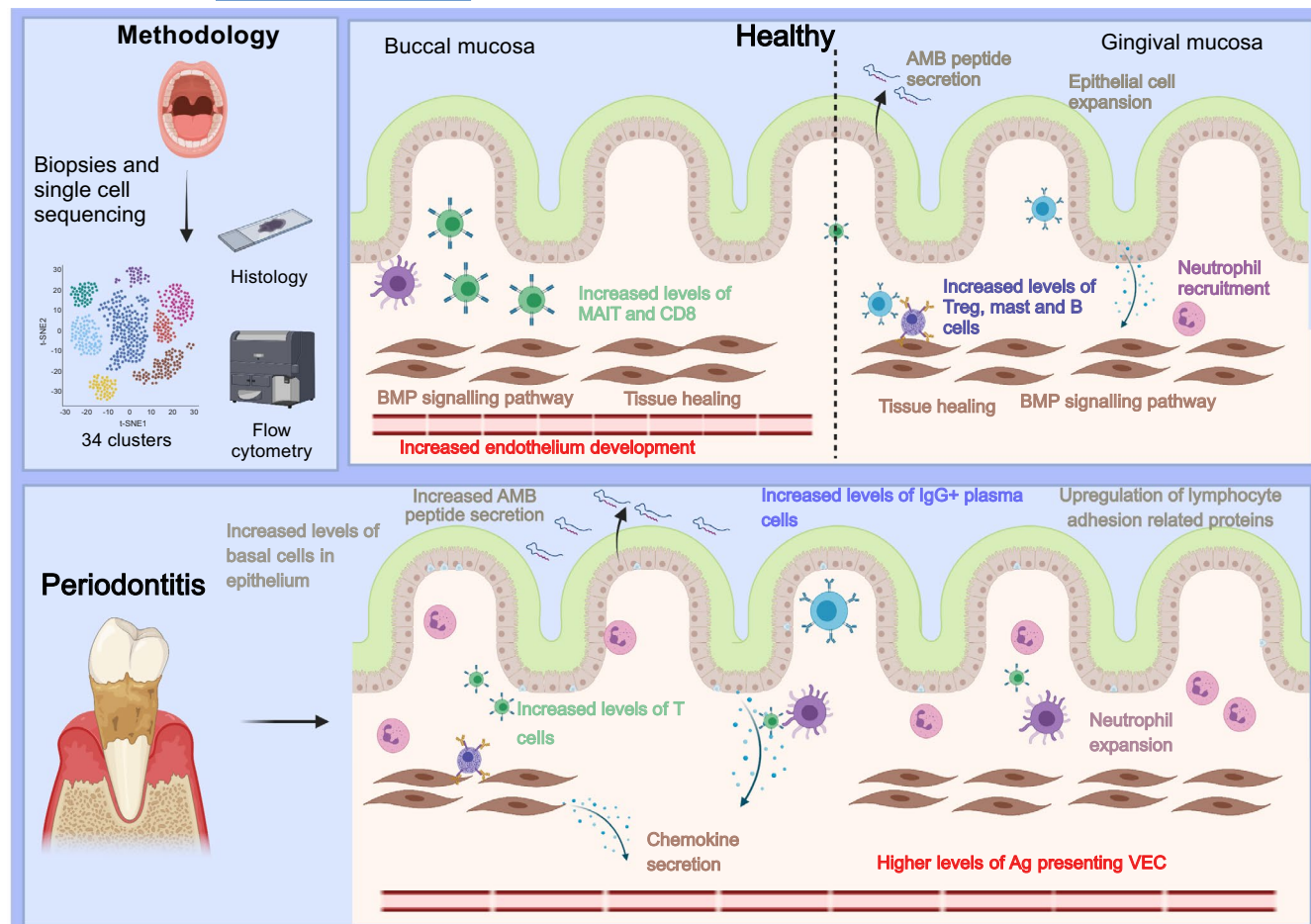


FIGURE 1 Main differences in healthy buccal and gingival mucosa, and in gingival mucosa with periodontitis. Summary of the findings of Williams et al² about oral mucosa composition. Briefly, biopsies from the buccal and gingival mucosa were isolated from healthy individuals and patients suffering from periodontitis. Characterization of cells was performed by single-cell sequencing, histology and flow cytometry experiments. Upper figure: the main findings in composition of buccal and gingival mucosa in healthy individuals are displayed. Buccal mucosa presented higher levels of MAIT and CD8⁺ cells, increased endothelium development and regenerative fibroblast phenotypes. On the contrary, gingival mucosa was characterized by inflammatory preparedness signatures such as antimicrobial peptide secretion, neutrophil recruitment and increased mast cells and B cells numbers. Lower figure: the inflammatory changes associated with periodontitis in the gingiva involve T cell and neutrophil infiltration and an increase in Ag presentation to immune cells. Figure created with <http://www.biorender.com>. Ag: antigen; AMB: antimicrobial peptides; MAIT: mucosa-associated lymphoid T cells; CD: cluster of differentiation; VEC: vascular endothelial cells; Treg: regulatory T cell; and Ig: immunoglobulin

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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