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Possible Existence of a Salivary Gland-Oral Mucosa/ Gingiva Axis Under Challenges by Endotoxins

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Abstract

In the submandibular salivary gland (SMG), endotoxins have been shown to induce inflammation cytokines and inflammatory proteins such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor–α (TNF-α), and calprotectin. Among them, the salivary gland inflammatory protein, calprotectin, is localized in the cytoplasm of the gland cells upon challenges made by endotoxins, and is not secreted into saliva, suggesting its protective function toward the gland cells. On the other hand, the precursor of IL-1β is localized in the secretory granules of the granular convoluted tubular cells in the SMG, and processed to generate active IL-1β, which is then secreted into saliva upon stimulation by endotoxins. Since the oral mucosal and gingival epithelia produce microbial peptides/proteins such as defensins, and its production is induced by inflammation cytokines, possible existence of a salivary gland-oral mucosal/gingival epithelia axis via salivary IL-1β is suggested, which helps induce anti-microbial peptides (defensins) in these soft tissues of the oral cavity.

Keywords: Salivary Gland; Endotoxin; IL-1β; Calprotectin; Defensins; Oral Mucosa; Gingiva

Abbreviations

IFN-γ: Interferon-γ; IL-1α: Interleukin-1α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; LPS: Lipopolysaccharide; PG: Parotid Gland; SMG: Submandibular Gland; TLR: Toll-like Receptor; TNF-α: Tumor Necrosis Factor–α

Introduction

In the mucosal membrane of the gastrointestinal tract and the oral cavity, the mucosal immune system is constructed where secretory IgA is released. In addition, invasive and pathogenic bacteria can be detected at the local site and anti-microbial peptides are promptly produced to initiate defense mechanism [1]. These antimicrobial peptides, especially those of the defensin family [2], have emerged as fundamental mediators among the innate mechanisms. On the other hand, antimicrobial peptides/proteins and secretory IgA are also secreted from the salivary gland [3]. Among them, cystatin, mucin, and defensins have both anti-bacterial and anti-viral activities. Peroxidase and histatin have anti-bacterial and antifungal activities, respectively. These salivary antimicrobial peptides/proteins are also essential for the mucosal membrane to protect the host from microbial infection. Recently, it has become apparent that interleukin-1α (IL-1α), IL-1β, tumor necrosis factors (TNFs), and interferon-γ (IFN-γ), while playing an important role in the response to microbial invasion, inflammation, tissue injury, and immunological reaction, are produced and/or secreted from the salivary gland. In this review the following explanation focuses on the induction and secretion of inflammation cytokines from the salivary glands and their pathophysiological linkage to a defense system in the oral mucosa and gingiva.

Endotoxin-Induced Production and Secretion of Inflammation Cytokines in the Salivary Glands

IL-1β is a polypeptide that is produced upon infection, injury or an antigenic challenge. A wide variety of cells in the epidermal, epithelial, lymphoid and vascular tissues synthesize this protein. On the other hand, the Toll-like receptor (TLR) superfamily has been defined, and continues to expand. Its members are known to participate in the host response to injury and infection [4,5], indicating their strong linkage to cytokines. Yao *et al.* [6,7] reported that the salivary glands as well as lachrymal glands in rats and mice expressed TLR4, and that mRNAs for several inflammation cytokines such

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as IL-1β, IL-6, and TNF-α were induced upon stimulation of the TLR4 by endotoxins, namely lipopolysaccharide (LPS) *in vivo*. The involvement of TLR4 in the induction of inflammation cytokines by endotoxins has been confirmed by using C3H/HeJ mice, which have a point mutation within the coding region of the *Tlr4* gene, resulting in a substitution of a highly conserved proline by histidine at codon 712, and therefore are endotoxin-resistant because of the lack of normal TLR4 functions [8]. Expression levels of mRNA for IL-1β and other inflammation cytokines (IL-6 and TNF-α) in the submandibular gland (SMG) are much higher than those in the parotid gland (PG) [6].

In the SMG, IL-1β is localized in the secretory granules of granular convoluted tubular cells [7]. Since these secretory granules contain growth factors and their binding proteins/processing enzymes or tissue kallikreins [9], it has been presumed that the precursor of IL-1β is processed within the granules. In fact, tissue kallikrein mK13 is shown to have an activity to process the precursor of IL-1β [10]. Thus a short and active form of IL-1β appears in the saliva upon LPS injection, indicating that this inflammation cytokine is secreted into saliva [7]. It is speculated that TNF-α and IL-6 are also secreted into saliva similarly to IL-1β, although further study is needed. Since the oral mucosal and gingival tissues of the oral cavity are exposed to saliva, these tissues are supposed to be directly affected by salivary components, suggesting the existence of a salivary gland-oral mucosa axis.

Expression of Calprotectin (S100A8/A9) in the Salivary Glands

Calprotectin is a member of the S100 protein family, predominantly expressed in the neutrophils, monocytes, myeloid cells, and activated macrophages [11]. It is a pleiotropic protein whose functions are associated with bacteriostatic effects and inflammatory processes [12]. The oral epithelia express calprotectin in severe periodontal diseases induced by periodontal pathogens of *Porphyromonas gingivalis* [13]. On the other hand, Javkhlan *et al.* (2011) have shown that both mRNAs and proteins for S100A8 and S100A9, the subunits of calprotectin, which will be designated as S100A8/A9 here after, are elevated by LPS in the SMG and PG of mice [14]. The response of S100A8/A9 to LPS are different from that of inflammation cytokines to endotoxins for the reason that LPS induced-S100A8/A9 are localized in the duct cells in the SMG and the duct and acinar cells in the PG, and that they are present in the cytoplasm in all these cells. Moreover, these proteins do not appear in the saliva upon LPS injection [14]. Thus salivary gland calprotectin would function within the gland cells or in the micro-environment near these cells to protect the tissue when an endotoxin has been challenged [15].

Production of Anti-Microbial Peptides/Proteins in the Oral Mucosal Membrane and in Gingival Tissue and their Induction by Inflammation Cytokines

Mucosal and gingival epithelia in the oral cavity are continuously exposed to various species of microbials. These tissues detect invasive/pathogenic microbials, and produce anti-microbial peptides/proteins as well as CXC type chemokines, by which a defense system is provoked [16]. Thus β-defensins and anti-microbial peptides are produced in oral mucosa and gingival epithelial cells [17,18]. Invasion of pathogenic microbes also affects the salivary gland because endotoxin administration induces inflammation cytokines and calprotectinin addition to β-defensins as mentioned above [17,18], Therefore, effects of salivary components cannot be ruled out from the possibility of its involvement in the defense mechanism in the oral mucosa and gingiva.

Conclusion

We hypothesize the existence of a salivary gland-oral mucosal/gingival epithelia axis *via* salivary inflammation cytokines although further study is required.

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