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Review Article

Regulation of defensive function on gingival epithelial cells can prevent periodontal disease

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Summary Periodontal disease is a bacterial biofilm-associated inflammatory disease that has been implicated in many systemic diseases. A new preventive method for periodontal disease needs to be developed in order to promote the health of the elderly in a super-aged society. The gingival epithelium plays an important role as a mechanical barrier against bacterial invasion and a part of the innate immune response to infectious inflammation in periodontal tissue. The disorganization of cell–cell interactions and subsequent inflammation contribute to the initiation of periodontal disease. These make us consider that regulation of host defensive functions, epithelial barrier and neutrophil activity, may become novel preventive methods for periodontal inflammation. Based on this concept, we have found that several agents regulate the barrier function of gingival epithelial cells and suppress the accumulation of neutrophils in the gingival epithelium. We herein introduce the actions of irsogladine maleate, azithromycin, amphotericin B, and *Houttuynia cordata* (dokudami in Japanese), which is commonly used in traditional medicine, on the epithelial barrier and neutrophil migration in gingival epithelial cells *in vivo* and *in vitro*, in order to provide support for the clinical application of these agents to the prevention of periodontal inflammation.

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Contents

1. Introduction

Periodontal disease is a bacterial biofilm-associated inflammatory disease that is caused by a shift in local microbial ecology [1,2]. Since periodontal disease has been implicated in many systemic diseases, such as diabetes mellitus, cardiovascular diseases, aspiration pneumonia, and dementia etc, its prevention is essential for the health promotion of the elderly in a super-aged society of Japan. Periodontal disease may be prevented via two strategies: (1) the removal of periodontal pathogens (bacterial biofilm) from periodontal tissue and (2) the regulation of host defensive mechanisms in periodontal tissue against periodontal pathogens. At present, the most effective and safest method for the prevention of periodontal disease is the mechanical removal of biofilms by self-care. However, physiological or psychological conditions in the elderly make this difficult. The chemical or biological methods to remove or eliminate selectively periodontal pathogens from the oral cavity have not yet to be established. On the other hand, fluoride treatment has beneficial effects like prevention of dental caries by shifting the balance from demineralization to remineralization. Based on the same concept as fluoride treatments, we have been developing an approach to the regulation of host defenses in periodontal tissue for the prevention of periodontal disease.

The gingival junctional epithelium is located at a strategically important interface at the bottom of the gingival sulcus and actively contributes to inflammatory processes. It plays a crucial role as a mechanical barrier against bacterial invasion and in the innate immune response to infectious inflammation in periodontal tissue [3–5]. Thus, the interaction between epithelial cells and periodontopathogenic bacteria has been suggested to be critically involved in the initiation of periodontal disease. The regulation of function of gingival epithelial cells may prevent the onset of periodontal disease.

Irsogladine maleate acts on gastric mucosal epithelium as an anti-gastric ulcer agent. Azithromycin has immunomodulatory properties with beneficial effects for lung diseases such as diffuse panbronchiolitis and cystic fibrosis. Amphotericin B has also shown to modulate host immune responses against fungal infections. *Houttuynia cordata* (dokudami in Japanese) is used internally and externally as a traditional medicine and has many pharmacological activities. These agents may have the potential to regulate gingival epithelial cell function for prevention of periodontal disease. Based on this concept, we demonstrated the role of the gingival junctional epithelium in periodontal disease and the mechanisms regulating the functions of gingival epithelial cell by several agents such as irsogladine maleate, amphotericin B, azithromycin, and *H. cordata*. In this review, we propose a novel concept for the prevention of periodontal disease.

2. Role of the junctional epithelium in the initiation of periodontal disease

Epithelial cells function as a mechanical barrier against invasion by pathogenic organisms and promote intercellular communication through cell–cell junction complexes, followed by the production of inflammatory cytokines and anti-microbial peptides. Multi-protein cell junction complexes are symmetrical structures that form between cells and are crucial for maintaining the physical and functional integrity of tissues. Epithelial cells are generally interconnected by tight junctions, adherence junctions, desmosomes, and gap junctions. However, the junctional epithelium in clinically healthy periodontal tissue is only interconnected by desmosomes and occasionally by gap junctions, and has wide intercellular spaces [3,5].

The initiation of periodontal disease is attributed to cleavage within the second or third cell layer of DAT cells (directly attached to the tooth) in the coronal-most portion of the junctional epithelium facing biofilms, and not to the detachment of DAT cells from the tooth [6,7]. Following the cleavage of the junctional epithelial surface, the secretion of cytokines and chemokines such as interleukin (IL)-8 results in the accumulation of neutrophils in the junctional epithelium, while proteases secreted by neutrophils disrupts the epithelial barrier of the junctional epithelium [8]. The accumulation of activated neutrophils in lesion areas

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