Role of Defensins in Oral Diseases: An Overview

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ABSTRACT

The oral cavity outreaches as a particular environment in which there is a continuous interplay between bacteria, fungi and viruses and the epithelial barrier. Among the innate mechanisms that aim to establish a regulated equilibrium between health and disease, natural antimicrobial peptides, especially those part of the defensins’ family, have emerged as fundamental mediators. Their biological role is emphasized by the large number of expressed genes as well as the multiplicity of the individual molecules present on biological tissues and fluids, in physiological and pathological conditions. Furthermore, the direct antimicrobial action, defensins may play a pivotal role in the orchestration of the innate response and contribute to the interplay between the innate and adaptive immunity. This review focuses on the specificities of defensins.

Keywords: Defensins, Precancerous lesions, Periodontitis, Pulpitis.

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INTRODUCTION

Epithelial surfaces are characterized by effective innate functions, which contribute to the protective purpose and favor the establishment of the regulated equilibrium between health and disease. The epithelial function is particularly relevant in the oral cavity that encloses a unique milieu, in which the mucosa fulfills a critical protective purpose by layering as an interface between the external and internal environment. The epithelial is not only a physical barrier, but also has chemical defense mechanisms containing antimicrobial peptides, such as defensins. Defensins are endogenous, small, cysteines-rich antimicrobial peptides that are produced by leukocytes and epithelial cells. Most defensins function by binding to the microbial cell membrane and once embedded, forming pore like membrane defects that allow efflux of essential ions and nutrients.

Molecular advances have revealed that these molecules include several germline-encoded pattern-recognition receptors (PRRs), which share several characteristics. These molecules are expressed by macrophages, neutrophils and dendritic cells, among others, and are responsible for the pattern recognition of broad classes of pathogens. Locally produced or systemic recruited chemical mediators may play an important role on the protection of the oral tissues against microorganism’s adhesion, proliferation and disease establishment; protection that is established within local, i.e. teeth, jaws, gingival and the remaining oral mucosa as well as systemic structures of the organism.

DEFENSINS

Defensins can be subdivided in two families, α- and β-defensins, which can be structurally characterized by a β-sheet-rich fold and a framework of disulfide-linked cysteines. Differences between the families are based on the length and the folding of the peptide chains, location and position of the cysteines residues in the amino acid sequence and the disulphide motifs, which are responsible for the pairing cysteines. α-defensins consists of 29 to 35 amino acids and are shorter β-defensins, which consists of 38 to 42 residues.

Substantial evidence has accumulated in recent years indicating that mammalian defensins are multifunctional and by interacting with host cell receptors, participate in both the innate and adaptive antimicrobial immunity of the host. In humans six α-defensins (HND1, HND2, HND3, HND4, HD5 and HD6) and four β-defensins (HBD1, HBD2, HBD3 and HBD4) have been defined. Polymorphonuclear leukocytes express α-defensins as part of their nonoxidative antimicrobial mechanism and β-defensins are expressed by mucosal epithelial cells.

α-defensins are essentially found on neutrophils and Paneth cells–specialized cells of the intestinal mucosa–while β-defensins are constitutively expressed in the epithelial compartment. Neutrophils have been characterized by the production of human neutrophils defensins 1 to 4 (HND1 to HND4), while human defensins 5 and 6 (HD5 and HD6) have been mainly associated with Paneth cells and the genitourinary tract. On the contrary, human β-defensins are generally found in association with epithelial surfaces, namely skin, gut, trachea and oral epithelium.

Searches of the human genome have revealed almost 40 potential coding regions for HBDs; however, only four (HBD1, HBD2, HBD3 and HBD4) have been characterized in detail. The localization of HBD1, HBD2 and HBD3 in stratified squamous epithelium (including oral mucosa and skin) has been confirmed at protein and mRNA levels. Human β-defensins 1 (HBD1) and HBD2 have been reported to be expressed in the skin, plasma, gut, saliva and stratified epithelium of the oral cavity. Some studies have suggested differences in the expression of HBD1 and HBD2.
at different sites in the oral cavity. While HBD1 was expressed in most locations in the oral cavity, HBD2 was only found in gingival tissues and especially in sites of inflammation. In gingival tissues HBD1 and HBD2 are localized in the sulcular epithelium, but not in the junctional epithelium. HBD2 is a major antimicrobial peptide that is produced by many types of epithelial cells, and is transcriptionally inducible by various proinflammatory agents, such as cytokines and bacteria.6

By contrast, HBD3 was mainly localized in the basal layer of the gingival epithelium, not only in the keratinocytes but also in Langerhans’ cells and Merkel cells, suggesting that HBD3 facilitates cross talk between the gingival epithelium and the connective tissues. HBD3 has been identified in muscular tissue, placenta, skin, as well as in trachea and crevicular fluid, following expression by oral keratinocytes. More recently, HBD4 has been characterized as an inducible tissue-restricted defensins, being expressed in genital-associated organs, thyroid, lung and kidney, following trigger by infectious processes.7

ANTIMICROBIAL AND IMMUNOLOGICAL ROLE OF DEFENSINS

For most defensins, an antimicrobial activity against several bacteria, mycobacteria and fungi has been reported. HBD1 and HBD2 are both active against Gram-negative bacteria and have a more limited activity against Gram-positive agents.8

Localization of HBD2 peptide in tissue sections of oral lichen planus, leukoplakia, candidal leukoplakia and radicular cyst was carried out using immunohistochemistry. HBD2 was stained in both the hyperkeratinized and the granular layers in cases of lichen planus with hyperkeratosis and leukoplakia. Expression in spinous and suprabasal layers was often strong in lichen planus. There were no significant differences in the number of S-100-positive dendritic cells between the widely stained areas and those with limited staining areas in lichen planus. In cases of candidal leukoplakia, the hyphae of Candida were mainly detected on the surface of keratinization, which showed only negative or faint staining for HBD2.9

These results suggest that HBD2 is vigorously induced by lichen planus-related inflammation and that it plays an important role in protection from Candida albicans infection; however, it is not a strong chemotactic attractant for Langerhans cells in pathological conditions of oral HBD1, HBD2 and matrix metalloproteinase (MMP)-25 and -26 expression in chronic and aggressive periodontitis and in peri-implantitis. The expression of MMP-25 by cultured human plasmacytoma cells and macrophages, and the effects of MMP-26 and Porphyromonas gingivalis trypsin-like proteinase on HBD1 and HBD2 were also found.10

While HBD3 has been shown to be highly active against Gram-positive microorganisms. They all have a marked antifungal activity, for instance against Candida albicans.8

The main mechanism by which the defensins exert their antimicrobial activity is the permeabilization of the targets’ membrane, which in bacteria has been shown to induce the inhibition of RNA, DNA and protein synthesis. Defensins have been characterized as inactivating agents of determined enveloped viruses, including role associated with HIV-non-progression.11

Defensins can also activate the classical complement pathway and have the potential to modulate the inflammatory response through the regulation of cytokine and adhesion molecule expression. Specifically, α-defensins are able to up regulate IL-8 expression, which is known to improve neutrophils recruitment to effector sites. Defensins may provide a link between the unspecific and adaptive response, α-defensins appear to attract both CD4 and CD8 naive lymphocytes and immature dendritic cells. β-defensins have been reported to be chemotactic agent for CD8 and CD4 memory T cells as well as to dendritic cells.12
DEFENSINS IN PERIODONTAL DISEASES

The expression of HBD1 and HBD2 in the gingival tissue of patients with gingivitis, aggressive periodontitis and chronic periodontitis was investigated. The results showed the differential expression of HBD1 and HBD2 genes in these groups of patients. Expression of HBD1 and HBD2 was lower in gingival tissues from patients with gingivitis than in the tissues from healthy controls, perhaps indicating an enhanced susceptibility of patients with gingivitis to periodontal infections.1

*Porphyromonas gingivalis*, one of the most pathogenic bacteria in chronic periodontitis, stimulates HBD2 expression in gingival epithelial cells, and this is markedly upregulated by the secretion of proteases by the organism through a protease-activated receptor pathway. Porphyromonas gingivalis along with *A. actinomycetemcomitans* are the most characterized pathogens which have established resistance to the activity of neutrophils’ α-defensins. Further *P. gingivalis* inhibits the expression of IL-8 by gingival epithelial cells, which decrease defensins’ efficacy by impairing neutrophils recruitment and consequent microbicidal peptide influx.13

Aberrant MMP and HBD functions have been found in inflammatory diseases. The objectives of this study were to investigate the immunolocalization, mRNA expression and molecular forms of MMP-25, MMP-26, HBD1 and HBD2 in chronic and aggressive periodontitis and in periodontal infections.14

DEFENSINS IN ORAL PREMALIGNANT LESIONS AND ORAL CANCER

A study investigated the gene expression of HBD1, HBD2 and HBD3 in oral squamous cell carcinoma (OSCC) compared to benign and premalignant lesions as well as healthy controls. Biopsies of healthy gingiva, irritation fibroma, leukoplakia and OSCC were obtained. HBD1, HBD2 and HBD3 were analyzed by real-time polymerase chain reaction. The expression of HBD1 was reduced in all lesions (5-fold in irritation fibroma and 2.5-fold in leukoplakia), but most significantly (50-fold) in OSCC. HBD1 appears to play a role in the development of OSCC. The loss of its function might contribute to the malignant progression of these tumors.15

Recently HBD3 has been found to have role in the progression of oral cancer. Premalignant cells in carcinoma *in situ* lesions overexpress HBD3, but not HBD1 and HBD2, correlate with specific recruitment and infiltration of macrophages.16 An *in vitro* studies demonstrate that HBD3 chemoattracts THP-1 monocytic cells and that epidermal growth factor (EGF) significantly induces HBD3 expression in oral epithelial cells via mitogen-activated protein kinase (MAPK) kinase MEK1/2, p38 MAPK, protein kinase C (PKC), and phosphoinositide 3 kinase (PI3K), but not via Janus kinase (JAK) and signal transducer and activator of transcription (STATs). These results suggest that HBD3 serves as a mitogen responsive gene in the initiation of oral cancer and may act as a motility signal to recruit tumor-associated macrophages.17

DEFENSINS IN SALIVA

Saliva contains several types of antimicrobial peptides, including defensins, which may have an important role in innate host defense. Many types of human defensins have been discovered and characterized in the last decade. Salivary defensins are possibly derived from salivary ductal cells, oral epithelial cells and some blood cells. The antimicrobial activity of defensins may be affected by the components of saliva. The HND1, HND2 and HND3 have been detected in saliva and may be derived from neutrophils. The HBD1 and HBD2 have been detected in saliva.18

Although it has been speculated that salivary HBDs are derived from keratinocytes that line the oral mucosa rather than from the salivary glands, the HBD 1 peptide was recently found to be specifically expressed in salivary ductal cells, although not in acini. Defensins may be useful for the treatment of periodontal disease and for the prevention of caries and periodontitis. Salivary defensin levels can be altered in oral diseases, and therefore may be a useful marker for risk assessment, salivary diagnosis and therapeutic strategies.19

DEFENSINS IN DENTAL PULP

A study was conducted to compare the gene expression of HBD1, HBD2, HBD3 and HBD4 in healthy teeth and teeth with pulpitis. Samples of healthy and inflamed dental pulps were obtained from extracted third molars and during treatment of teeth with pulpitis. It was noted that HBD2 and HBD3 were only weakly expressed in healthy and inflamed pulps. In contrast, the expression of HBD1 and HBD4 was significantly increased in inflamed compared with healthy pulps. These results suggest that HBD1 and HBD4 might play a role in the pulpal host defense.20

CONCLUSION

Nevertheless, much has yet to be learnt regarding the proper biological role of defensins in the oral environment, it is becoming clearer that these antimicrobial peptides play a major function in the biological modulation of the response to commensal and pathogenic agents. Current evidence justifies their primary role in the direct antimicrobial defense
although additional role in the regulation of the innate and inflammatory responses are being progressively established.

REFERENCES


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