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Review Article

Cathelicidins in the Oral Cavity- Unravelling the mystery

Deepak Narang[1], Manmeet Kaur[2], Shama Shishodiya[3], Fatima Khan[4]

[1]PG teacher Oral Medicine, Prasad Medical College Saraishazadi, Banthara, Kanpur Road, Lucknow, U.P., India
[2]Associate professor, Department of General Pathology, GGS Medical College & hospital, Faridkot, Punjab, India
[3]DNB ENT & Otolaryngology, Chacha Nehru Bal Chikitsalya, Delhi
[3]Reader OMDR, Rungta Dental College KohkaKurud (Bhillai), Chhattisgarh, India

***ABSTRACT*:**
Cathelicidins are a group of oral antimicrobial peptides that play multiple vital roles in the human body, such as their antimicrobial (broad spectrum) role against oral microbes, wound healing, and angiogenesis, with recent evidences about their role in cancer regulation. Living in the era where the major focus is on non-invasive and nanotechnology, this ultimately leads to further advancements in the field of salivaomics. In this article, we have highlighted the importance of cathelicidins in the oral cavity.
Key words- Antimicrobial, Cathelicidins, Nanotechnology.

Corresponding Author: Dr. Deepak Narang, PG teacher Oral Medicine, Prasad Medical College Saraishazadi, Banthara, Kanpur Road, Lucknow, U.P., India

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INTRODUCTION

The human body is exposed to harsh environmental conditions and various infectious diseases. Infectious diseases are the global cause of mortality and morbidity. The host's immune system plays a vital role in protection. There are various levels of immunity such as innate factor, adaptive immunity and anatomical and physiological barriers. Innate immunity can be further categorized into humoral immunity and cellular mechanisms. In addition, a part of innate factor is build up from a broad research methods have used antimicrobial peptides as a tool to combat against intruding pathogens, and, hence, is renowned as natural antibiotics. The in vitro experiments using AMPs displayed a wide range of antimicrobial activity.[1]

Human Cathelicidin (LL-37)

Cathelicidin family of antimicrobial peptides consists of a "cathelin" domain at their N terminus and a mature peptide at their C terminus. The amino acid sequence of the cathelin domain is highly conserved and thereby similarity is observed despite species or cells it is obtained from. The mature peptide however demonstrates considerable variation in its size, amino acid sequence, and three-dimensional structures. The cathelin domain derives its name from a porcine neutrophil protein of the same name, since both share sequence homology. The only antimicrobial peptide of Cathelicidin family expressed in humans is LL-37. It was cloned from human bone marrow cDNA and derives its name from its length of 37 amino acids with two leucine residues in the beginning.[2]

Cathelicidins (LL-37) is an antimicrobial peptide that belong to the cationic amphipathic family found in both mammals (such as rabbits, cattle, horses, pigs, rats, rodents, and ungulates) and non-mammal. In mammals, LL-37 are produced by various cells, including skin epithelial cells, leukocytes, B-cells, keratinocytes, melanocytes, neutrophils, bone marrow cells, breast milk, mast cells, seminal plasma, salivary glands, inflamed gingival tissues, and respiratory epithelium. Hence, cathelicidins are among the first defence peptides that come in contact with foreign pathogens and aids in first line defence.[3]

Types and Biochemistry of LL-37

Cathelicidins and their precursor molecules are synthesized after proteolytic cleavage. Based on their

structures and molecular weight diversities, these peptides are characterized and are found in a variety of species. The particular gene that is reported to be responsible for the synthesis of cathelicidins in mammals is organized as 4 exons and 3 introns. Four other different genes (CATH1, CATH2, CATH3 and CATH-B1) have been reported in birds that have structure similar to mammalian peptides. Three genes (CATH1, CATH2, CATH3) encodes for the major part of cathelin-like domain, signal peptides and 50 untranslatedterminal. While the fourth exon (CATH-B1) encodes for mature peptides and 30 untranslated terminals.[4]

Cathelicidins are generated as inactive precursor molecule comprises of three parts;

(1) N-terminal that is composed of 29–30 amino acid molecules and is assumed to guide the liberation of biologically active peptides;

(2) cathelin-domain comprising of 98–114 amino acid molecules with its function not yet examined.

(3) C-terminal that comprises of 12–100 amino acid molecules as an active peptide with wide range of antimicrobial property against bacteria, viruses, and fungi.[5]

The reported members of cathelicidins family include;

- LL-37 (leucine-leucine 37) that is found in humans,
- CRAMP (cathelicidins related antimicrobial peptide) found in rats and mice,
- Flow licidin and cathelicidins -1 found in chickens,
- CATH-1 and CATH-2 both are found in the Atlantic salmon,
- p15s found in rodents, and CAP18 in rabbits
- CAP11 is found in guinea pigs and LL-37 in rhesus monkeys.[6]

Structure

The cathelicidin gene in humans is translated into an inactive precursor protein termed as hCAP-18. Upon posttranslational processing an active C terminus peptide with 37 amino acids is released from precursor protein. This cleavage is carried out via proteolytic enzyme elastase or proteinase-3. This peptide has a net positive charge at physiologic pH and more than 50% of its residues are hydrophilic in nature. Structurally, it exists as a random coil in aqueous solutions. Many of its amino acids form intramolecular hydrogen bonds, acquiring anα-helix secondary structure. It is supposed that antibacterial activity of LL-37 is correlated with α-helicity.[7]

Gene Encoding LL-37

The gene encoding LL-37 is located on chromosome 3 at location 3p21.3. It has been named cathelicidin antimicrobial peptide (CAMP) gene. LL-37 gene has four exons and three introns. First three exons encode for the signal sequence and cathelin region of the peptide while the fourth exon translates into mature peptide. In intron and promoter region of LL-37, there exist binding sites for acute phase response factors, which establish the upregulation of LL-37 in inflammation.[8]

Induction of Gene Expression

LL-37 expression in various cell types has been found to be upregulated on exposure to growth factors, differentiating agents, and microorganisms. Insulin-like growth factor-1 which is known to promote wound healing upregulates LL-37 expression. Also, vitamin D which is a differentiating agent has been found to amplify LL-37 activity. Increased level of LL-37 in gingival tissues in response to inflammation correlates positively with depth of gingival crevice. In a comparative study, levels of LL-37 in GCF were found to be significantly elevated in chronic periodontitis patients than in gingivitis patients and healthy volunteers.[9]

Mechanism of Action against Microbes

Antimicrobial peptides are components of host defence proteins that act against the microbial invasion by various mechanisms, such as: (a) barrel-stave model; (b) carpet model; and (c) toroidal model. A comprehensive review on oral antimicrobial peptides, their types and role in the oral cavity, including how these peptides are secreted and inhibit bacterial activities, has been reported elsewhere.[10] Cathelicidins and other antimicrobial peptides exhibited the potential of eliminating foreign pathogens through various processing pathways such as membrane disrupting activity, antiseptic activity, apoptosis, angiogenesis, wound healing, chemotaxis and immune modulation (both humoral and cellular components). Furthermore, these peptides target only pathogens, not human cells, due to the diversities within the biological membrane, including structure and composition. The broad spectrum antimicrobial property of cathelicidins is because of their ability to disrupt the bacterial cell membrane and ultimate death of bacteria. The three mechanisms proposed on how these peptides act on cell membranes include carpet model, barrel stave, and toroidal pore models.[11]

Other Roles

LL-37 acts as a chemoattractant and causes influx of neutrophils, monocytes, and T cells to the site of inflammation. Some researchers believe that it acts as an "alarmin" rather than an antimicrobial by enhancing the immune response leading to activation of antigen presenting cells.[12]

Importance of LL-37 in Oral Cavity

The environment contains an infinite number of microorganisms. For instance, bacteria are covering our skin, throat, gut, nasal cavity, ear, eyes, and oral cavity. LL-37 act as a broad-spectrum antibiotic in the human body.[13] It was reported that this peptide provides essential role in innate response against Mycobacterium

tuberculosis, as they stimulate alveolar macrophages as first line of defense against tuberculosis. Another important role of cathelicidins is that it inhibits certain gastrointestinal (GI) disorders, such as ulcers, inflammation, and cancer, as these conditions commonly invade GI mucosa. Bacteria associated with gastritis and peptic ulcers are killed, which helps in repairing and angiogenesis of damaged tissues.[14]

LL-37 has an immunomodulatory effects comprised of cellular and humoral components. The cellular component stimulates cells that play a crucial role in immunity and killing of foreign pathogens, for instance: neutrophils, macrophages, mast cells, dendritic cells, monocytes, and eosinophils.[15]The humoral component (includes proteins, complement system and cytokines, cathelicidins) plays a different role.

LL-37 also increases chemotaxis activity and migration of neutrophils by inhibiting expression of surface receptors CXCR2. One of the principal mechanisms of innate immunity in which neutrophil extracellular traps (NETs) is formed (NETosis), cathelicidins aids to the formation of these NETs.[16] LL-37 affects other inflammatory cells activity as well, which includes monocyte or macrophages. In these cells it is also reported that they enhance the receptor expression on the site of injury, stimulate mediator release, aids in decreasing the endotoxin of Neisseria meningitis.

LL-37 is seen to be expressed in tongue and buccal mucosa, and also can be detected in GCF and saliva. While, inflamed gingival tissues have shown to have upregulated expression of LL-37, signifying its diagnostic activity in inflammatory periodontal disorders. The role of LL-37 in saliva suggests its antimicrobial activity in the protection of tooth structure, which, in turn, can be correlated to resistance to caries.[17]

Cathelicidins are well known for innate defensive barrier against various microbial pathogens, including gram negative and gram positive bacteria. Murakami et al.[18] investigated the expression of messenger RNA of cathelicidins in the sialadenitis through reverse transcriptase-polymerase chain reaction and immunohistochemically staining. Cathelicidins protein expressions are upregulated in chronic sialedinitis compared to normal salivary glands and providing defense mechanisms in the salivary glands. Moreover, cathelicidins has been broadly studied in relation to their immunomodulatory and antibacterial properties, whereas, salivary LL-37 is also being released by neutrophils in gingival crevicular fluid, salivary glands, and expressions of LL-37 indicates its role in the protection of tooth structure, oral mucosa, and enhances the production of immunoglobulins (IgA and IgG).[19]

CONCLUSION

Cathelicidins is a group of antimicrobial peptides that are secreted in the oral fluids, such as saliva, gingival crevicular fluid and can be used for diagnostic significance of oral health. The enhanced level of oral cathelicidins is associated with inflammatory conditions, such as gingivitis and immune disorders, such as oral lichen planus.

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