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Review Article

A Comprehensive Review of LL-37 in Periodontal Disease

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Abstract:

Human cathelicidins (LL-37) are an exceptional class of host defense peptides which are small, cationic, and amphipathic in nature with pleiotropic functions such as antimicrobial, chemotactic, and immunomodulatory functions. This peptide is synthesized as pre-propeptide with a signal peptide, an N-terminal cathelin domain (13.5 kDa) connected to a highly variable antimicrobial domain at C (carboxyl) terminal (4.5 kDa). These proteolytically activated peptides form a part of innate immunity functions as the first line of host defense against numerous microorganisms and join hands with other innate defenders to combat bacterial attack and colonization. In addition to antimicrobial activity, LL-37 also participates in the activation of specific immune responses in the host. Many *in vitro* and *in vivo* studies have shed the light into the pivotal role played by LL-37 in maintaining the health of the periodontium. Apart from antimicrobial activity, LL-37 exerts its protective effects on the periodontium by its antibiofilm activities, neutralizing the lipopolysaccharide of periodontal pathogens, antiosteoclast properties, and immunomodulatory effects such as neutrophil chemotaxis. LL-37 with the magnificent properties certainly takes part in curtailing the periodontal pathogens and restraining the progression of periodontitis. Studies on patients who lack LL-37 have demonstrated the occurrence of aggressive forms of periodontitis. This points to the fact that these patients are deprived of the protective functions of LL-37. Accordingly, LL-37 is an antimicrobial peptide that plays a vital role in keeping the microbial challenges (especially of the periodontal pathogens) at bay thereby functioning as elemental molecules of innate immunity in periodontal disease. This review provides an insight into the antibiofilm, anti-endotoxin, and antibacterial effects of LL-37 on periodontal pathogens.

Key Words: Antimicrobial, cathelicidin, LL-37, periodontal disease

Introduction

Periodontitis is defined as a chronic inflammatory disease, polymicrobial in nature resulting in inflammation and destruction of attachment apparatus. Hence, the periodontium is under constant surveillance by the immune system of our body so that the bacterial challenge can be kept at bay.[1,2] Besides serving as a physical barrier, the oral epithelium joins hands with innate immunity by producing cytokines and antimicrobial peptides (AMPs), thereby dampening the uncontrolled inflammatory response in periodontal tissues.[3,4] The AMPs forms an evolutionarily conserved weapon of innate immunity and cathelicidins are one among such AMPs expressed ubiquitously possessing not only antimicrobial activity but also immunostimulatory and immunomodulatory functions along with angiogenic properties.[5]

This review focuses mainly on structure and expression of human cathelicidin (LL-37) with special emphasis on its antibiofilm, anti-lipopolysaccharide (anti-LPS), and antibacterial effects on periodontal pathogens.

Human Cathelicidin (LL-37) and its Structure

Cathelicidins are small, cationic amphipathic peptides, expressed in epithelial cells, and defense cells such as neutrophils, lymphocytes, natural killer cells monocytes, and macrophages. Cathelicidins belongs to an enormously versatile class of host defense peptide of oral cavity that forms an indispensable innate immunity weapon in the frequently bacterial challenged oral environment. Cathelicidins such as many of the other AMPs are pleiotrophic in nature as they possess antimicrobial, chemotactic, and immunomodulatory functions.[6,7] They find their space in the secondary granules (peroxidase-negative) of neutrophils and macrophages and are concerned with non-oxidative killing of pathogens. Unlike in other species, humans express only one cathelicidin known as LL-37, in which 37 denotes the length of the peptide and "LL" signifies the first two amino acids formed by Leucine. It is also known by the names hCAP18/CAMP/FALL-39. The gene encoding LL-37 (CAMP-cationic AMP) can be localized to chromosome 3 (3p21) with four exons and three introns. Of the four exons, the first three are involved in coding the signal peptide and cathelin domain, whereas the fourth exon encodes the processing site and variable C-terminal AMPs.[4,8,9]

Based on the structure and as evidenced by circular dichroism, Fourier transform infrared spectroscopy and nuclear magnetic resonance (NMR) spectroscopy studies, LL-37 acquires a linear cationic amphipathic α-helical structure in the presence of bacterial membrane for the expression of its antibacterial action and host immunomodulatory activities.[6,9] Cathelicidins are synthesized as a pre-propeptide with a signal peptide, an N-terminal which is evolutionally conserved cathelin domain (13.5 kDa) connected to a highly variable antimicrobial domain at C-(carboxyl) terminal (4.5 kDa), by name LL-37 (in humans), imparting antimicrobial and immunomodulatory activities to cathelicidin.[7] The antimicrobial domain is bonded to the cathelin domain by aminoacids, which are cleavage sites for specific enzymes such as neutrophil elastase, cathepsin G, and proteinase 3.[10] After exclusion of signal peptide, cathelicidins (hCAP18) remain as inactive proforms in the secondary granules of neutrophils to be released at sites of inflammation.[11] In humans, proteinase 3 attacks the cleavage site between Ala-Leuaminoacids and makes available the mature AMP (LL-37) from the cathelin domain for microbicidal activity.[4,11] Hence, LL-37 can be considered as the C-terminal mature AMP of 37 amino acids (C-terminal peptide) with distinct antimicrobial activity. The functions of cathelin domain remained obscure until a study by Zaiou *et al*. provided evidence to its role in bacterial inhibition and in regulating cysteine-proteinase-mediated tissue damage.[12]

When viewed through NMR LL-37 is composed an N-terminal α-helix separated by a bent from a C-terminal α-helix and a C-terminal tail and denoted as helix-bend-helix conformation. The concave surface is connected to four aromatic phenylalanine side chains and encircled by positively charged residues. Thus, a net positive charge is maintained by cathelicidins that is essential for its antimicrobial activity.[6] The simultaneous occurrence of hydrophobic and hydrophilic residues confers an amphipathic nature on the peptide which is crutial for its penetration of the bacterial membrane. The cationicity of the peptide makes its interaction with negatively charged molecules such as LPS possible, and the hydrophobic nature can be regarded as a doorway to diffuse through the phospholipid bilayer.[6,13]

Expression of LL-37 during Periodontitis

The cathelicidins are expressed ubiquitously and ever since its discovery from the bovine derived myeloid cells has fuelled substantial interest in the field of research. The ever-presence of this peptide in many organisms suggest the evolutionarily conserved nature of the peptide and is thought of to play a crucial role in innate immunity involved in setting up of a relentless resistance to the bacterial attack. In humans, LL-37 is expressed (either constitutive or inducible) in leukocytes, epithelium of respiratory tract, urinary tract, and GIT and also in the skin and in most body secretions, including sweat, breast milk, and saliva. The widespread distribution of this peptide in inflamed tissues points to their involvement in the protection of host tissues from microbial infections.[6,10,14] Puklo *et al*. analyzed the GCF content of LL-37 in healthy, chronic, and aggressive periodontitis patients and concluded that neutrophils are the main source of hCAP/LL-37 in healthy periodontium, whereas in patients with periodontitis other cells apart from neutrophils contribute to local production of LL-37.[8] Consequently, it can be assumed that a deficiency/defect in cathelicidin secretion, as in morbus Kostmann syndrome and Papillon-Lefèvre syndrome, may increase the susceptibility to infections including chronic periodontal infections.[4,15] In conjunction with this LL-37 also possess the ability to modulate neutrophil response to bacterial challenge highlighting the importance of this peptide in the host responses during periodontitis, especially aggressive forms of it.[4,15-17]

It has been shown that LL-37 expression increases with increase in severity of periodontal disease.[14] Furthermore, a positive correlation has been established between the LL-37 levels and gingival sulcus depth.[3,14] A logical explanation for this could be that when inflammation sets in the periodontium, the oxygen content is significantly reduced rendering the oxygen mediated killing of PMNs ineffective. Such a situation calls for non-oxidative killing facilitated by AMPs such as LL-37.[8] Usually, LL-37 is present at a concentration of 2-5 μg/ml and in sites of inflammation concentration (inflamed epithelium) becomes as high as 30 μg/ml.[18] In healthy subjects, LL-37 is found at a salivary concentration of 0.5 μg/ml and GCF concentration of 10 μg/ml in periodontitis patients.[19]

Recently, it has been proved that vitamin D plays an important role in the regulation of cathelicidin expression. Vitamin D results in up regulation of cathelicidin, since the cathelicidin gene contains vitamin D response element sequence in its promoter region. On the contrary, during the periods of inflammation, vitamin D acts to down regulate the expression of cathelicidin. Furthermore, a c-AMP signaling pathway is concerned with the constitutive expression of LL-37 in epithelial cells.[6]

LL-37 and Bacterial LPS

Cathelicidins have a broad spectrum of activity against Gram-positive and Gram-negative bacteria including major periodontal pathogens, such as *Porphyromonas gingivalis, Prevotella intermedia,* and *Aggregatibacter actinomycetemcomitans,* along with other microorganisms such as fungi and viruses.[20-22] LPS, from Gram-negative periodontopathic bacteria, is a major virulence factor that has the ability to induce cytokine production.[23] This cytokine induction is triggered off when the lipid domain of LPS (a bacterial endotoxin) binds with LPS-binding protein[24] and transfers LPS to its receptor CD14 present on the surface of mononuclear phagocytes resulting in the activation of nuclear factor-κB (NF-κB) transcription factor and p38 mitogen-activated protein kinase mediated production of inflammatory cytokines.[23]

Furthermore, the miraculous ability of LL-37 in neutralizing the bioactivity of LPS safeguards the tissues from the harmful effects of LPS.[24,25] This anti-LPS activity is primarily by curtailing cytokine induction and endotoxin mediated proinflammatory responses via mechanisms such as binding to and competing with LPS for the binding site within the CD14 receptor[26] and dampening of LPS-induced translocation of NF-κB. Besides, LL-37 maintains a balance between pro- and anti-inflammatory mediators during LPS challenge.[25] Accordingly, LL-37 can be looked upon as an anti-endotoxin and LPS neutralizing factor.[23,25,26]

In addition to this the cationic peptide exerts direct bactericidal effects on bacteria by targeting LPS and teichoic acid of Gram-negative bacteria and Gram-positive bacteria, respectively.[6] Upon on contact, LL-37 is inserted into the bacterial membrane triggering cell rupture and leakage of cytoplasm. Several models have been proposed to an account for this peptide-bacterial membrane interaction, namely barrel-stave model, toroidal model, and carpet model. In the barrel stave model, the peptides are arranged like a barrel ring, and the membrane channel formed is described as a barrel stave with the hydrophobic surfaces of the peptide facing the membrane, whereas the hydrophilic surface lines the pore.[27] The toroidal model advocates that LL-37 once attached causes bending of the lipid monolayers with the core lined by a head group of both the peptide and the lipid layer.[28] The carpet model involves the accumulation of LL-37 around the membrane with resultant membrane disruption without pore formation. Together with carpeting of the membrane, the intracellular structures, such as DNA, seem to bind with LL-37 and are known as Shai Matsuzaki Huang model.[6,27,28] This antimicrobial activity of LL-37 is ascribed to domain specificity of parent LL37 with its LPS neutralizing property contained in the middle portion, i.e., (amino acids [AA] 104-140 of the human cathelicidin AMP).[29,30] Studies were conducted to find out means by which the LPS neutralizing and antibacterial activity could be enhanced. Nagaoka *et al*. used LL-37 as a template and as a short fragment peptide (18-mer; K15 to V32 [K15-V32] displayed LPS neutralizing activity similar to that of parent LL-37 and that enhancing the hydrophobicity and cationicity of this 18-mer peptide resulted in augmentation of the LPS-neutralizing property.[21] Paradoxically, in the process of disrupting bacterial membranes, LL-37 has shown to be lytic to erythrocytes as well, that is, it lacks cell selectivity. It is believed that the presence of sialic acid in the erythrocyte membrane puts it at a risk for LL-37 attack.[6] Thennarasu *et al*. in his study on LL-37 proved that the residues 7-27 of LL37 was responsible for the desired antimicrobial activity, and the residues 1-6 and 28-37 played a role in lytic activity against erythrocytes and LPS detoxification. This non-hemolytic LL-37 derived peptide was named as LL7-27.[31]

The antibacterial effects of LL-37 are inhibited to a certain extend by bacterial polysaccharides, mucins, host, bacterial proteases glycosaminoglycans, and high salt concentration.[29,32,33] When compared to other AMPs, LL37 may be less susceptible to enzymatic degradation as it can form dimeric and trimeric aggregates in solution, and the diluting effects of saliva aids in keeping the salt and inhibitor concentrations to a minimum favoring antimicrobial action of LL-37.[31,34]

Cathelicidins and Antibiofilm Activity

Biofilm can be considered to be composed microcolonies of bacteria which are safeguarded by self-secreted slimy extracellular polymeric substances surrounding the microcolonies[28] to survive adverse environmental conditions and is a bacterial mechanism to evade the host defense mechanism.[18] Dental plaque is an oral biofilm with its vast array of bacterial species (especially the red complex consisting of *P. gingivalis*, *Tannerella forsythia,* and *Treponema denticola*) beyond any doubt has proved to be the cause of inflammatory process such as periodontitis and is constantly being put on a check by the body's innate immune system.[35,36] The use of conventional antibiotic therapy usually fails when it comes to eliminating biofilm bacteria mainly due to the inability of antibiotics to penetrate the biofilm and the development of highly resistant bacterial species. Under these circumstances, AMPs such as LL-37 have evolved as a novel therapeutic agent with antibiofilm properties, especially at low concentrations to combat the biofilm bacteria.[28]

LL-37 accomplishes the antibiofilm effects by decreasing the adherence of the bacteria to tooth surface by regulating the quorum-sensing-dependent genes required for biofilm formation and also by interfering with the thickness of biofilm by increasing the surface motility of bacteria (twitching).[18,37,38] Biofilm bacteria are metabolically less active to evade the activity of antimicrobial agents; however, they are vulnerable to LL-37.[38] By preventing the biofilm formation, the bacteria are exposed to and rendered susceptible to the body's immune responses.[39] LL-37 has found to be possessing antibiofilm activity against bacteria such as *Pseudomonas aueroginosa*, *Burkholderia pseudomallei*, *Streptococcus mutans*, *Staphylococcus epidermidis*.[38,40,41]

LL-37 and Major Periodontal Pathogens

LL-37 has shown to be protective against dental plaque bacteria,[8] and many *in vitro* studies have focused on the inhibitory effect of LL-37 on oral bacterial species including *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia,* and *Fusobacterium nucleatum*.[42] The hCAP-LL-37 gene is stirred by many of these pathogens and along with the neutrophil invasion into the periodontal pocket at times of inflammation results in increased local availability of cathelicidins for combating the bacterial challenge.[8]

A. actinomycetemcomitans and LL-37

There is a large body of evidence stating the consistent relationship between AA and aggressive (ESP localized

aggressive) periodontitis. This tissue invading anaerobic bacteria escapes the killing mechanisms of the epithelium and gradually gains ability to survive in the intracellular environment. Recent data has pointed out that ORF859 gene favors the organism for its intracellular homeostasis.[43] Proliferation of AA in patients with neutrophil defects or a deficient secretion of LL-37 has been associated with aggressive periodontal disease. LL-37 was shown to be acting as an opsonin rendering AA to the phagocytic clearing by neutrophils and monocytes. The ability of LL-37 to exert antibacterial action against AA suggests a potential involvement in aggressive forms of periodontitis.[44]

P. gingivalis and LL-37

A special feature of *P. gingivalis* is that it a tissue penetrating bacteria and is a highly proteolytic organism that degrades a variety of AMPs including LL-37.[45,46] The ability of *P. gingivalis* to produce arginine-specific gingipains, and the unique LPS composition makes it resistant to activities of LL-37.[46,47] Thus, the inhibitory effect on LL-37 may be regarded as a virulence mechanism of *P. gingivalis* in the pathogenicity of periodontal disease.[14]

T. denticola

Previous studies have showed that LL-37 is ineffective against systemic spirochetes. LPS is the prime target of most of the AMPS including LL-37, but *T. denticola* (oral spirochete) lacks true LPS. Notwithstanding, LL-37 binding to MSP of *T. denticola* triggers the bactericidal activity. Besides, dentilisin is inhibited by saliva, and LL-37 attaches to MSP before dentilisin could degrade LL-37, thus escaping from the degrading effects of dentilisin.[19,34]

T. forsythia

This red complex bacteria releases a metalloproteinase, karilysin which dampen down the antibacterial and anti-inflammatory properties of LL-37 for safe and easy survival in the dental plaque.[15]

In view of all the studies relating to LL-37 and oral plaque bacteria, it can be noticed that LL-37 exerts the maximum inhibitory effect on primary colonizers, i.e., the yellow-orange complex, whereas the pathogenic red complex was resistant to the activities of LL-37. This might be the reason for the preponderance of these periopathogens in the pathogenesis of periodontitis.[34]

Conclusion and Future Directions

LL-37, with its magnificent antibacterial, antibiofilm, and anti-osteoclast properties,[34] certainly takes part in curtailing the periodontal pathogens and restraining the progression of periodontitis. This is evidenced from the occurrence of aggressive forms of periodontitis in patients with defective neutrophils with resultant LL-37 deficiency. These patients lack the advantage of the biologic functions of LL-37 preventing them from mounting an effective resistance to periodontal pathogens. Furthermore, recently, a novel biological function of LL-37 has been brought to light that is LL-37 inhibits osteoclast generation. Thus, it is worthwhile to conclude that LL-37 deficiency has a significant role in pathogenesis of periodontitis.[34] Further studies are needed to understand the functions of LL-37 on a molecular level, especially the antibacterial effects on planktonic and oral biofilm bacteria and for commercially producing LL-37 to be used as a local drug delivery agent for direct effect in the periodontalpockets.[4,34]

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