WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 4, 142-147. Review Article ISSN 2277–7105

UNRAVELING THE ROLE OF ANTIMICROBIAL PEPTIDES IN PERIODONTITIS- A CONCISE REVIEW

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Article Received on
23 December 2023,
Revised on 13 Jan. 2024,
Accepted on 03 Feb. 2024
DOI: 10.20959/wjpr20244-31249

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ABSTRACT

Immune responses are protective responses by the host to the presence of invading organisms, their antigens, and their toxins. Periodontal health is maintained by a delicate balance by the host immunity with the maintenance of the immune response in an impeccable homeostatic state. A wide variety of host proteins have been shown to have antimicrobial activity. Antimicrobial peptides like defensins, cathelicidin, saposins, histatin and many others will come under immune proteins. Antimicrobial immune proteins play a major role in acting as the first line of epithelial defense and this review discusses some of the host proteins with its antimicrobial activity.

KEYWORDS: Periodontitis, Antimicrobial peptides, Defensins.

INTRODUCTION

Antimicrobial peptides have multiple functions in host defence. The Defensins are the best characterized antimicrobial protein molecules & are considered to be a microchemokine that acts on cells of the adaptive immune system.[1,2] Among the antimicrobial peptide family, small cationic defensins represent an important peptide. There are two subfamilies in defensins, the α-defensins & β defensins. They are distinguished on the basis of the connectivity of their six cysteine residue. Later the cyclic theta defensin was identified from leukocytes. First β defensin was isolated from the tongue mucosa. Subsequently, 13 novel β defensins were purified from neutrophils. The human β defensin 1 (hBD-1) was purified from hemofiltrates and was later found in urine as a Gram-negative bacteria killing antibiotic.

Distribution

The oral, sulcular and junctional epithelium of the gingiva are all associated with Defensin expression. Because they are the discrete area of the underlying connective tissue associated with Polymorphonuclear leukocytes.[3] The β defensins hBD1,2,3 are all found in the oral and sulcular epithelium and are absent in junctional epithelium. The mRNA of β defensin is principally expressed in the supra basilar layer of the healthy sulcular epithelium. Human β defensin 1 & 2 are more in the spinous layer but the peptide is found mainly in the upper spinous and granular layer. The human β defensin 2 seems to be found slightly more suprabasally than the human β defensin1. This distribution was similar in both healthy and inflamed gingiva.

Expression

In the most epithelium including healthy gingiva, human β defensin 1 is constitutively expressed and at the same time, human β defensin 2 appears to be highly Inducible. The second human β defensins (hBD-2) is expressed in all inflammations and is induced by TNF α and IL1 β. Both human β defensins show microbicidal activity predominantly against Gram-negative bacteria like porphyromonas gingivalis, Fusobacterium nucleatum.[4] Human β defensins expression is regulated by inflammatory stimuli at a transcription level. Alpha-defensins have the ability to attract T cells; Human β defensins attract immature dendritic cells and memory T cells via chemokine receptor.[5] This provides a link between innate defence and adaptive immunity. Based on the tertiary structure, defensins can be classified into two subfamilies, human α defensin, and human β defensin. All the defensins are with 3 disulfide bonds via a pair of cysteine residues and that is the characteristic feature of defensins. The human α defensin have 29 to 35 residues and β human defensins have 38 to 42 amino acids. These small molecules have an intricate tertiary structure with a core of 3 antiparallel β sheet components resembling chemokines.

Cathelicidin (LL 37) consists of the linear C terminals of the human CAP 18 molecule. It has an alpha helical structure, it interacts with formyl peptide receptor-like 1 (FPRL1), G protein-coupled receptor.

Storage and Release

The α defensins are otherwise known as the human neutrophil peptides (HNP - 1). They are largely stored in the granules of neutrophils and to a lesser extent in the macrophage.[6]

Chemotactic activities of defensins

Defensins play a role in assisting other parts of the innate immune response and altering the adaptive immune response. They are directly involved in the anti-microbial killing. They also interact with various receptors on immature dendritic cells and lymphocytes, resulting in activation of adaptive immune response. It is mainly based on chemotactive effect of antimicrobial peptides for selected leukocytes. Defensins are chemotactive for those cells that express the appropriate receptors. Defensins can attract host cells by expressing the appropriate receptors along the gradient to their site of origin.[7]

Alpha defensins are capable of activating the classical complement pathway and it up-regulates the interleukin-8 production via increased gene transcription by epithelial cells.[8] This in turn enhances neutrophil recruitment to the site of infection. Alpha defensins are chemotactive for immature dendritic cells and some CD8-T lymphocytes but not neutrophils or monocytes. The receptor for alpha-defensins has been identified as a G & I protein-coupled receptor.

The alpha defensins interact with the G protein coupled receptor for the adrenocorticotrophic hormone, which may account for their capacity to suppress glucocorticoid production. This suppressive effect promotes the immune enhancing capabilities of alpha defensins.

The β defensins are selectively chemotactic only for CCR6 expressing cells, inducing immature dendritic cells and resting memory CD4, CD45RO as well as some CD8 T lymphocytes. Chemotactic effects of cathelicidin are predictable. It interacts with FPRL1.

Because of their cationic and amphiphilic characteristics, antimicrobial peptides bind and insert into cytoplasmic membrane. The bactericidal activity could also results from electrostatic charge based mechanism of membrane permeabilization rather than a mechanism based on the formation of membrane permeabilization.

Microbicidal activities of Defensins & Cathelicidin

Alpha defensins

Alpha defensins degranulate mast cells resulting in to release of histamines. Systemic cellular & humoral responses are enhanced by administration of alpha defensins. This is associated with enhanced production of both Th1 & Th2 type cytokines such as IL1, TNF, IL6, IL4 & Interferon-gamma. Human alpha defensins have potent immunoadjuvant effects & systemic

injections of human alpha defensins results in augmentation of both Th1& Th2 immune responses to potent as well as weaker tumor antigens.

Human beta defensins

They are chemotactic for subsets of T cells & immature dendritic cells that express CCR 6. They promote adaptive immune mechanism. Beta defensins facilitate the delivery of antigen to receptors on immature dendritic cells. Beta defensins use TLR4 to induce Th1 immune responses independent of its CCR6 dependent chemotactic effect.

In health, gingival epithelial cells do not express human β defensin 2, but on stimulation with bacterial products and cytokines, there is an up-regulation of human β defensin 2 mRNA. It is particularly in case of Fusobacterium nucleatum, but not for Porphyromonas gingivalis. Induction of human β defensin 2 in response to Fusobacterium nucleatum has shown to be independent of the NF & Kappa B ligand pathways of osteoclasts activation and instead relies on MAP kinase pathway activation.

Pathogen cell wall lysisShai-Mat Suzaki Huang model broadly expresses the activity of most of the anti-microbial peptides, because the exact nature of the interaction between defensins and bacterial cell wall is not determined. The selectivity for bacterial cell wall relies on the outer bilayer of their cell membrane.[9] Usually, the negatively charged phospholipids are found on the cytoplasmic side of the bilayer. Initially, electrostatic attraction occurs, and then followed by the displacement of the membrane lipids in a wedge-like a manner. Depending on the molecules and the bacterial cell wall, the mechanism differs. But the end result is disruption of the microbial cell wall, resulting in the leakage of the cytoplasmic content. In some cases, the defensins may have specific intracellular targets.[10]

Immune responses are protective responses by the host to the presence of foreign substance like invading organisms, their antigens, and their toxins. Periodontal health is maintained by a delicate balance by the host immunity in which pathogen co-exists with the host. Disruption of balance causes the alteration in both the host and biofilm resulting in the destruction of the periodontium. Functional neutrophil or macrophage defects in chemotaxis predispose to periodontal diseases. The antimicrobial immune proteins play a major role in acting as the first line of defense in the gingival sulcus. By complementing the adaptive cellular immune system, by offering an immediate host response, by preventing the activation of immune cascade responses with their untoward efforts, the antimicrobial immune protein acts as the

first line of epithelial defense. In future, inducible, epithelial Antimicrobial Peptides may prove to be a vital advance in dealing with infection.

Cathelicidin: In a mouse model of septicaemia, LL-37 binds to and neutralizes LPS and protects against endotoxic shock.[11] Histatin has a protective role in periodontal diseases by inhibiting proteases of P.gingivalis.

Action of antimicrobial peptides

Antimicrobial peptides are small chemotactic proteins of cationic charge involved in host innate immune defense.

Acute inflammation

The killing of bacteria, releases the bacterial inflammatory mediators (LPS, LTA), regulation of macrophage response, adherence of PMN and chemotactic stimulation of mast cells to release histamine. Fibroblast growth adherence, apoptosis of viral or bacterial infected host cells, inhibition of fibrin clot lysis (thereby limiting bacterial spread), inhibition of proteases (thus limiting tissue injury).

Chronic inflammation

Recruitment of T cells, enhancement of monocyte chemotaxis, regulation of macrophage response. Antimicrobial peptides are found in oral mucosa and in neutrophil granules and act on phospholipids on the cell membranes via positively charged domain. Defensin molecules insert into membranes, where they interact with one another to form pores that disrupt membrane function leading to cell killing. Due to the higher concentration of negatively charged phospholipids in bacterial membrane, defensins preferentially bind to and disrupt bacterial cells.

Clinical application

Antimicrobial peptides are tested in clinical trials for the treatment of Acne, oral candidiasis. Bacteria have evolved countermeasures to the action of antimicrobial peptides – (changes in wall composition, transporter system).

CONCLUSION

Periodontal health is a state of balance in which the pathogen co-exists with the host. Alterations in the balance result in a destruction of periodontal health. In future, inducible, epithelial antimicrobial peptides may prove to be a vital advance in the development of novel

strategies for antimicrobial therapy. By epithelial peptide antibiotic synthesis, i.e., artificial defensins for local application in the area prone to refractory gingivitis and periodontitis proves its microbicidal activity.

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