REVIEW ARTICLE

Defense Mechanisms of Gingiva

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ABSTRACT

Defense is resisting an attack; there are numerous protective mechanisms that work in the oral cavity against various insults. Gingiva is constantly subjected to a wide array of mechanical, chemical and antigenic challenges—some of which are transient and others permanent. This review will discuss how the gingiva prepares and safeguards itself via diverse defense mechanisms in the face of this challenging environment.

Keywords: Gingival defense mechanism, Protective mechanisms in gingiva, Gingival crevicular fluid.

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INTRODUCTION

By failing to prepare, you are preparing to fail. Gingiva prepares and protects itself from various pathogens, through the fine tuning of homeostasis. If this balance is lost, the activity of gingival tissue becomes abnormal, and this change is perceived as periodontal disease.[1] Defense mechanisms guarding the gingiva can be classified into—nonspeci fic and specific mechanisms (Flow Chart 1).[2] Nonspecific mechanisms include innate immunity and are the first line of defense. All infections cannot be prevented by innate immunity as microorganisms evolve rapidly.[2] To counter these changes, specific protective mechanisms of adaptive immunity enable the body to differentiate between 'self' and 'nonself'.

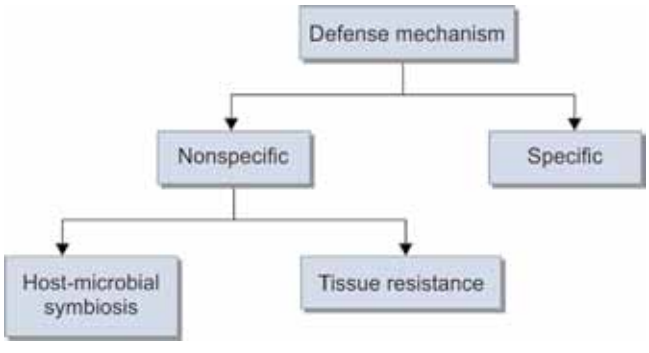
DISCUSSION

Nonspecific mechanisms that protect gingiva include host-microbe symbiosis and tissue resistance. Host-microbe symbiosis is a close, prolonged association between two or more organisms of different species, regardless of the benefit to the members. Most bacteria-host interactions are now believed to be nonpathogenic and both the host and bacteria benefit from peaceful co-existence.[3] Presence of 'friendly' commensal habitants is essential for mounting a well established host immune system that contributes to a healthy periodontium by protecting it from pathogenic microbes. The constant 'appropriate' innate response of gingiva to these commensal microbes (beneficial oral biofilm) thereby protects the periodontal tissues.[2,3]

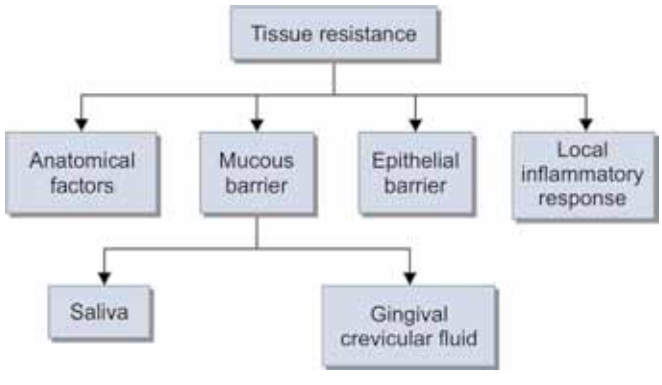
Tissue resistance (Flow Chart 2) consists of four barriers—anatomical factors, mucous barrier, epithelial barrier and local inflammatory barrier. A breach in one or more of these can cause disease.[6]

Anatomy of gingival tissues is designed for effective mastication and clearance of food debris.[6,8] Any poor functional tissue relations lead to plaque accumulation.[6] Stippling is a functional adaptation to provide resistance to mechanical trauma.[8] Attached gingiva is contoured to allow for proper deflection of food and is critical for maintenance of gingival health.[8] Gingival fibres that brace the marginal gingiva firmly against tooth surface, provides necessary rigidity to combat forces of mastication and tends to throw

Flow Chart 1: Classification of defense mechanism in gingiva



Flow Chart 2: Tissue resistance



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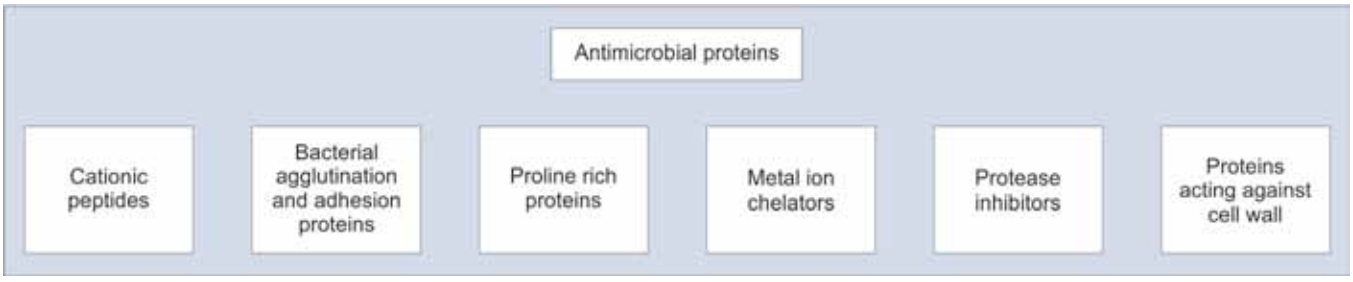
Flow Chart 3: Subclasses of antimicrobial proteins



out any foreign material into the sulcus.[4,6,8,9] This expulsion is aided by the movement of teeth and gingival tissues during function of dentition and pulse beats.[9]

Mucus barrier is formed by saliva, washing the gingival surface and gingival crevicular fluid (GCF), flowing through junctional epithelium (JE) into the gingival sulcus.[2,6] Saliva is the muco-serous secretion contributed by salivary glands.[2,6,7] Glycoproteins and mucoids in saliva, coat the gingival surface providing lubrication and physical protection.[1,6,7,10,11] Salivary flow influences calculus formation and thus gingival health.[7] This flow cleanses the gingival surface by cleaning debris and bacteria.[6,7] Bicarbonates and phosphates act as antacids neutralizing acidic bacterial products.[7] Coagulation factors VIII, IX and X, plasma thromoboplastin antecedent, Hageman factor in saliva, speed up coagulation and protect wounds from bacterial invasion.[7] Host defense molecules found in saliva including the host's innate and acquired immune responses, such as antimicrobial peptides, chemokines, cytokines, etc. have a major role in determining microbial balance and bacterial colonization.[3,6,10]

Antimicrobial peptides (Flow Chart 3) are early responders of innate immunity that 'search and destroy' the invading pathogens.[10] Cationic peptides may be bactericidal or bacteriostatic.[10] While no activity has been reported against *Candida albicans*, adenomedullin has shown to protect against Gram positive and Gram negative bacteria suggesting that it contributes to the mucosal host defense system.[10] Alpha-defensins[5,10] (human neutrophil peptides1-4) and Beta defensins[3,5,10,12] (hBD1, hBD2, hBD3) expressed in the gingival epithelium act as broad spectrum antibacterials, binding to or inserting into the bacterial cell membrane causing cell lysis. Also, Cathelicidin,[10] a precursor of antimicrobial peptide LL-37 ligates to and neutralizes lipopolysaccharides in Gram negative bacteria and *C. albicans*. Salivary-5-histatin[10,13,14] involved in generation of reactive oxygen species also binds to fungal cell membranes and enters the cytoplasm targeting the mitochondria inducing non-lytic cell death. Statherin,[10] another antimicrobial peptide, inhibits growth of anaerobic bacteria, and prevents crystallization of calcium phosphate thereby inhibiting calculus formation. Bacterial agglutination and adhesion proteins include mucin-7, salivary agglutinin and surfactant protein-A that are involved in bacterial binding and agglutination thus promoting bacterial clearance.[10] According to recent studies, they also block HIV from entering into host cells.[10] Proline rich proteins (PRP) are unique, since they may be both beneficial and harmful as the larger proteins promote the attachment of bacteria to the pellicle and thus induce plaque formation while the smaller ones inhibit their attachment.[1,10] Proline rich proteases in commensal bacteria degrade PRP and the end products limit bacterial adhesion.[10] Fibronectin reduces bacterial adhesion to oral surfaces by causing bacterial agglutination. It also inhibits the fimbrillin-induced expression of inflammatory cytokines in macrophages by directly binding to the fimbrillin from *P. gingivalis*.[10]

Metal ion chelators, e.g. calgranulin A and B and lactoferrin are cation scavengers that inhibit bacterial growth. Calprotectin, a dimer of calgranulin A and B, chelates with manganese and zinc ions.[10] Lactoferrin binds with two ferric ions along with a bicarbonate ion and acts on bacteria, viruses, fungi and parasites, killing *A. actinomycetemcomitans*, inhibiting the growth of *P. ginigivalis* and inhibiting the adhesion of *P. intermedia*, *P. nigrescens* and *A. actinomycetemcomitans* to fibroblasts.[1,10]

Generated by the host and bacteria, proteolytic enzymes in saliva initiate and contribute to the progression of periodontal diseases. Their action on target tissues is inhibited by Protease inhibitors.[10] Cystatins C and S are cysteine protease inhibitors that inhibit the growth of *P. gingivalis*.[10] Secretory leukocyte protease inhibitor, an antibacterial and anti-inflammatory protein, inhibits the action of bacterial serine protease enzyme.[10] Elafin has anti elastase activity.[10] Lactoperoxidase and myeloperoxidase belonging to heme peroxidise family form a major part of peroxidase system of saliva that catalyzes the oxidation of thiocyanate forming hypothiocyanite, and oxidation of chloride and iodide ions forming bactericidal end products.[1,10]

Another group of proteins are the ones which act against the bacterial cell walls. Lysozyme hydrolyses the (1,4)-beta linkages between NAM and NAG residues in peptidoglycans, mainly in the gram positive bacterial cell walls, making them more permeable.[1,10] Peptidoglycan recognition

proteins[1,3,4] present in saliva are bactericidal for pathogenic and non-pathogenic Gram positive bacteria by binding to the peptidoglycan. However, unlike lysozymes, they do not permeate the cell walls.[10]

Gingival crevicular fluid (GCF), another component of the mucosal barrier,[2,6] is an altered inflammatory exudate that flows into the oral cavity from the gingival crevice.[2,5,7,11] However, compared to saliva, the non-specific antibacterial mechanism offered by GCF consists of a more complex array of immune components.[1] GCF is derived from the gingival capillary bed as well as the resident and migrating inflammatory cells.[1,5,7] GCF flow increases during inflammation and thus may be considered as a way of throwing out the toxins and bacteria from the gingival sulcus.[5,7,9] It lubricates foreign materials to facilitate their expulsion.[9] It contains antimicrobial proteins, similar to those found in saliva.[1,3,5,7,10,12,15] It also contains inflammatory immune cells that contribute to local immune regulation through many mediators, including prostaglandin, leukotrienes, IL-1, IL-6, TNF and IL-8 and humoral antigenic activity.[1,2,4,5,7,9,15-17]

The epithelial barrier is a continuous epithelial sheath consisting of gingival, sulcular and junctional epithelium through which crowns of teeth protrude into the oral cavity.[2,6,10,12-14,16,17,19] An intact epithelium prevents frank bacterial invasion of periodontal tissues and is also effective against penetration of metabolic and bacterial components under normal health conditions.[2,4-7,9-11,16] Turnover rate, the rate at which all the cells in the tissue can be replaced is high at 41 to 57 days for gingival, 10 to 14 days for sulcular and 4 to 6 days for junctional epithelium, which allows for the rapid replacement of cells and tissues that are injured by pathological microorganisms.[2,4-7,9,10,11,16,18] Desquamation, the process wherein the dehydrated and flattened cells of the superficial layers are lost and replaced by cells of the underlying layers, limits the colonization of epithelial surface by pathogenic microorganisms, removes the bacteria that have already colonized and regenerates an intact epithelial barrier.[2,4-6,8-11,16,18]

A protective surface coverage is provided by the outer barrier of keratinized gingival epithelium and an inner barrier of epithelial attachment.[2,4-6,8-11,16,18] Epithelial attachment, formed by superficial flattened layer of JE in contact with the tooth surfaces and the inner basal lamina, together provide the attachment of gingiva to the tooth surfaces thereby preventing the growth and apical migration of bacterial plaque into gingival connective tissues.[2,4-6,8-11,16,18] This attachment is reinforced by gingival fibers, referred to as dentogingival unit.[14] The JE allows bidirectional movement of various compounds between the gingival connective tissue and oral cavity.[2,4-6,7,9-11,16] It is nonkeratinizing, being undifferentiated even in the coronal layers.[4,5,8,18] The lack of extensive intercellular connections and the presence of fewer intercellular adhesions and gap junctions provide it with abundant intercellular spaces. These spaces act as a GCF reservoir, becoming larger during inflammation and getting infiltrated with neutrophils, monocytes and lymphocytes. This prevents bacteria from penetrating the epithelium and producing a diffusion barrier to microorganisms, bacterial enzymes, metabolic by-products and other antigenic substances.[2,4-6,8-11,16] These spaces also produce a diffusion pathway for GCF and its constituents. Another special protective role of JE that has been recently reported is its endocytic capacity, similar to that of macrophages and neutrophils.[2,5,8,19] These cells are found to contain lysozyme like bodies and they engulf bacteria.[2,5,8,19] Epithelial cells have also been found to express antimicrobial peptides like beta-defensins, catheliciden, c-c motif chemokine 28, calgranulin A and B, lactoferrin, peptidoglycan recognition proteins 3 and 4.[3,4,5,7,10,15]

Local inflammatory response is the most significant and final barrier to penetration of connective tissue by bacteria and their toxins.[2,6] This response is stimulated by tissue injury and infection.[2] A series of reactions brings about local changes like increased vascularization leading to increased fluid collection and cellular exudation that eventually causes accumulation of serum proteins and phagocytic cells in the affected area.[2,16]

Keratinocytes, no longer considered as passive bystanders, play an active role in the activation of inflammation within the gingival tissues.[4,5,8] They synthesize a number of cytokines, adhesin molecules, growth factors and enzymes.[4-7,10] They also produce Interleukin 1, TNF, prostaglandin E2, matrix metalloproteinases, that diffuse through JE, enter the gingival connective tissue and initiate the cellular immune reaction.[4-7,10] Recruitment of neutrophils into the JE is mediated by antigen presenting cells (Langerhans cells), and adhesion molecules secreted by keratinocytes, promoting diapedesis of neutrophils along the chemical gradient.[5-7,10,19] Fibroblasts in the connective tissue are also involved in bringing about local inflammatory response.[1]

Neutrophils and macrophages are the two most important phagocytes that consume bacteria to protect the host tissues.[2,4-7] Neutrophils, the most predominant inflammatory cells in periodontal sulci, are important in maintaining the health of periodontium.[2,4,5] PMNs adhere to the host substrate, migrate to the site of infection along the chemical gradient, recognize the bacteria, and bring about phagocytosis.[2,5] Cytoplasmic processes or pseudopodia engulf and integrate the pathogen forming a phagosome.[5] Phagosomes then fuse with lysosymes to form phagolysosome wherein digestion and destruction of pathogen takes place. PMNs also undergo degranulation and allow extracellular killing of pathogens which is considered a principle mode of reducing bacterial count in the gingival crevice. The granules found

in PMN consist of primary (azurophilic) and secondary (specific) granules.[5] These can bring about oxygen dependant or independent plaque reduction.[5]

Macrophages have two protective roles — as phagocytes, and as antigen presenting cells.[2,5] The former engulf foreign material while the latter present the antigens on their cell surface thereby activating T-cells and providing cellular immunity.

Specific mechanisms: The body produces antibodies specific to a particular antigen. These antigens have 'flags' (specific amino-acid sequences) that help the immune system to recognize the 'non-self'.[2] After the lymphocyte gets exposed for the first time to the antigen, the lymphocyte memorizes the antigen encountered so that a consequent exposure will result in a faster secondary response of to the antigen.[2] Saliva and GCF contain immunoglobulin G, M and A that are synthesized locally as they bind exclusively to the strains of bacteria native to the mouth. IgA, IgG and IgM along with complements and PMNs bring about opsonization.[2,4-7]

CONCLUSION

The proper course of action, when under attack is usually to counterattack. The oral cavity is well equipped to counterattack any adverse condition that may harm the gingiva. While the innate immunity acts primarily against any foreign invader, the specific immunity takes a more complex targeted approach to protect the gingiva. Right from its superficial epithelial layer to the innermost connective tissue, there is a line of defense that acts in harmony with other oral structures to maintain homeostasis to revert any imbalance that would otherwise shift the equilibrium to the diseased state.[6]

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