



International Journal of Applied Dental Sciences

ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2018; 4(4): 30-35
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www.oraljournal.com
Received: 05-05-2018
Accepted: 07-06-2018

Dr. Probal Soud

a) Lecturer, Department of Periodontics and Oral Implantology, Nobel Medical College Teaching Hospital (Pvt.) Ltd., Biratnagar, Nepal
b) Post Graduate, Department of Periodontology and Oral Implantology, Rajasthan Dental College and Hospital, NH-8, Bagru Khurd, Ajmer Road, Jaipur, Rajasthan, India

Dr. Neha Yadav

Post Graduate, Department of periodontology and oral implantology, Rajasthan dental college and hospital, NH 8, Bagru khurd, Ajmer road, Jaipur, Rajasthan, India

Dr. Pradeep Kumar

Professor, Department of periodontology and oral implantology, Rajasthan dental college and hospital, NH 8, bagru khurd, Ajmer road, Jaipur, Rajasthan, India

Correspondence

Dr. Probal Soud

a) Lecturer, Department of Periodontics and Oral Implantology, Nobel Medical College Teaching Hospital (Pvt.) Ltd., Biratnagar, Nepal
b) Post Graduate, Department of Periodontology and Oral Implantology, Rajasthan Dental College and Hospital, NH-8, Bagru Khurd, Ajmer Road, Jaipur, Rajasthan, India

Fundamentals of Immunology and Periodontal Disease – Revisited

Dr. Probal Soud, Dr. Neha Yadav and Dr. Pradeep Kumar

Abstract

Periodontal disease is recognized as a major public health problem throughout the world and is the most common cause of tooth loss in adults. Although periodontal disease is of microbial etiology, the determination that periodontal tissue destruction is primarily due to the host response, has created areas of research directed at altering an individual's reaction to the bacterial challenge. This article is focused in discussing, in brief, the basics and application of the concept of immunology in periodontology. This article is aimed at reviewing the basics of Immunology which is an extremely important aspect of medical science and related to every individual's Health and Disease. Important aspects such as immunity itself, cells of the immune system, MHC and HLA systems, leukocyte functions, molecular biology, inflammatory mediators of the immune system and immunological aspects of periodontal diseases have been reviewed. A glance through this article may potentially revitalize and refresh the foundations of immunology in the reader's mind quickly.

Keywords: Immunology, periodontal disease, host response, cells of the immune system, MHC and HLA systems, leukocyte functions, molecular biology, inflammatory mediators, periodontitis, gingivitis

Introduction

Periodontal disease is recognized as a major public health problem throughout the world and is the most common cause of tooth loss in adults. Although microorganisms produce enzymes and other factors that can directly cause degradation of periodontal tissues, the progression and severity of tissue destruction are mostly caused by host immune responses to infecting bacteria. Protective aspect of host responses includes recruitment of neutrophils, production of protective antibodies and possibly the release of anti-inflammatory cytokines. Perpetuation of host response due to a persistent bacterial challenge disrupts homeostatic mechanism and release of mediators including proinflammatory cytokines, proteases (e.g., Matrix Metalloproteinases) and prostanoids (e.g., Prostaglandin E2 (PGE₂)) which can promote extracellular matrix destruction in the gingiva and stimulate bone resorption. The determination that periodontal tissue destruction is primarily due to the host response, has created areas of research directed at altering an individual's reaction to the bacterial challenge. This article is focused in discussing in brief, the basics and application of the concept of immunology in periodontology.

Classification Immunity can be broadly classified as innate immunity and acquired immunity. Innate immunity is further regulated by anatomic (skin, mucous membrane), physiologic (temperature, pH, chemical mediators), phagocytic and inflammatory barriers. Acquired immunity is further classified as natural and artificial immunities. Natural immunity can be passive (maternal) and active (infection). Artificial immunity can again be passive (Ab transfer) and artificial (immunization).

Innate and acquired immunity: Innate immunity provides the first line of defense against infection. Anatomic barriers includes Skin that consists of two layers, thinner outer epidermis and thicker inner dermis, Mucosal membranes which consists of an outer epithelial and inner connective tissue layer. Some of the internal mucosal membranes are provided with cilia which entrap and eliminate the invading organisms through their beating activity, Epithelial tissue which constitutively express antimicrobial peptides (e.g., Human beta defensins (hBDs) and LL-37) and secrete interleukin-8 (IL-8) and other chemokines and cytokines to alert various cell types^[1]. Physiological barriers include Temperature - Fever response inhibits

growth of some more temperature resistant bacteria, pH of less than 4 kills most of the ingested microorganisms, Soluble molecules like *Lysozyme* (mucous secretion & tears) cleaves bacterial cell wall, *Interferon* (protein produced by virus infected cells) induces antiviral state in uninfected cells, *Complement* (group of serum proteins which circulate in an inactive condition) lyses microorganisms or facilitates phagocytosis, *Collection* (surfactant proteins) disrupt bacterial cell wall, *Cell associated Molecules* exhibit the phenomenon of *pattern recognition* (i.e. ability to recognize a given class of molecules) Examples-Toll-like Receptors (TLRs). Inflammatory barriers refer to the complex sequence of events that induce immune response against invading pathogen or injury to the tissues. Saliva is produced in mouth by salivary glands and is a major component of innate immunity which helps protect the host with its flow-related and biochemical properties. Gingival crevicular fluid (GCF) is a transudate that originates from the postcapillary venules of the gingival plexus. It has a flushing action in the gingival crevice but also likely functions to bring the blood components (e.g., neutrophils, antibodies, and complement components) of the host defenses into the sulcus^[2].

Acquired immunity does not come into play until there is an antigenic challenge to the organism. Adaptive immunity responds to the challenge with a high degree of specificity as well as the remarkable property of 'memory'. Adaptive immunity exhibits four characteristic attributes namely: Antigenic specificity - the ability to distinguish even minute difference between antigens, Diversity - enables immense diversity through innumerable antibodies once the immune system has recognized and reacted to an antigen, Immunologic memory - available throughout the life of the individual and a second encounter will be responded with intense and immediate reaction and Self - non-self discrimination of molecules.

Cells of the immune system^[3]

The principal cells of the immune system are derived from the lymphoid and myeloid arms of the hematopoietic system. In the bone marrow, the myeloid arm gives rise to *peripheral dendritic cells (DCs)*, *phagocytes (neutrophils and monocytes)*, *mast cell precursors*, *basophils*, *eosinophils*, *platelets* and *erythrocytes*. In the tissues, peripheral DCs, monocytes, and mast cell precursors further differentiate. The monocyte can become a macrophage. In the bone marrow, the lymphoid arm gives rise to natural killer (NK) cells, *B cells* and *pre-T cells*. The pre-T cells differentiate to *T cells* in the thymus. Secondary lymphoid organs (including lymph nodes and the spleen) are areas where antigen-presenting cells, B cells, and DCs present antigen to T cells. Terminal differentiation of B and T cells also occurs in these organs.

Mast cells – They are major effectors of immediate hypersensitivity (allergic) reactions. Mast cells are derived from the marrow; resides in most of the tissues very close to blood vessels.⁴They contain cytoplasmic granules filled with effect or mediator molecules. There are two major subsets of mast cells - *Tissue and mucosal mast cells* which differ in their anatomical distribution, granule contents and activities.

Basophils – They are non phagocytic cells and fight against foreign molecules or microorganisms by releasing their cytoplasmic granules which contain pharmacologically active components. They are mainly concerned with allergic responses.

Eosinophils- They are primarily responsible for extra cellular killing of large parasites which cannot be phagocytosed.

However, they also exhibit phagocytic activity to a smaller extent.

Dendritic cells – They are the component cells of the innate immune system that are present in basal and supra-basal layer of oral mucosal epithelium. These antigen presenting cells capture microbial antigens in their immature state and stimulate a T-cell response to these antigens in their mature state. Dendritic cells participate in pathogenesis of periodontal disease by utilizing three mechanisms: 1. Modulation of adaptive response, 2. Direct interaction to the bacterial signals, 3.Capability to influence other cells and ultimately the immune response. DCs have been found to serve a role of surveillance by migrating in and out of oral mucosa under controlled by chemokines like Macrophage inhibitory protein - MIP-3 α and MIP-3 β and their receptors CCR6 and CCR7 respectively.

Macrophages -They are mononuclear phagocytic leucocytes, some of which are migratory and others are confined to particular tissues.⁵Macrophage population in a particular tissue is maintained by three mechanisms: 1. Influx of monocytes from circulating blood, 2. Local proliferation and 3. Biological turnover. Inflammatory macrophages: Occurs in various exudates and are characterized by specific markers (peroxidase activity). They also act as rapid protective mechanism which can respond before T cell-mediated amplification has taken place.

MHC and HLA Systems: The Major Histocompatibility Complex (MHC) participates in the development of humoral and cell mediated immune responses. MHC molecules are a complex of surface glycoprotein molecules on which the antigens bind to for recognition by the T cell receptor. This function of the MHC molecule is also called "antigen presentation". MHC is referred to as the HLA Complex in human. The loci of the HLA complex may be divided into three classes: Class I, Class II, and Class III. The products of Class I and Class II genes are called class I and class II MHC molecules respectively.

Neutrophils: They are active phagocytic cells and constitute the majority among. They are granular leucocytes possessing multilobed nucleus, primary azurophilic and secondary granules which stain with neutral dyes. The granules contain peroxidase, alkaline and acid phosphatases and defensins. They possess receptors for chemoattractant factors from microbes (e.g. Muramyl dipeptide or MPD) and complement components activated by microbes acting via Fc gamma - receptor binding to the Fc component of immunoglobulins (mainly IgG). Once recruited, the neutrophil phagocytosis accessible microbes in a process mediated by surface pattern recognition receptors (e.g. toll-like receptors) and/or IgG receptors (Fc gamma-RII and Fc gamma-RIII) into a phagosome. Once formed, the phagocytic vacuole receives a lethal payload of lysosomal (granule-derived) enzymes, cathelicidin antimicrobial peptides and reactive oxygen species to effect microbial destruction. From the bone marrow they are released into the circulation actively where they move for 7-10 hrs before migrating into the tissues, where they live for few days.

Lymphocytes: Interleukin-7 (IL-7) is a major factor in stimulating bone marrow stem cells to start down the path leading to the various lymphocytes (mostly B cells and T

cells). On the basis of their function and cell membrane components (surface markers), Lymphocytes are of 3 types-T cells, B cells and Natural killer cells (NK cells)

T-cells: T-cells are important component of cellular adaptive immunity and various different sub-sets of T-cells have been found in periodontal tissue and these sub-sets depended on various factors like are T-cell repertoire, HLA systems, antigen-recognition, specific recruitment process into respective lesion, interaction with antigen presenting cells, costimulatory molecules expressed locally, environmental cytokines and peripheral regulation by regulatory T cells. These cells induce direct attack and lysis of infected cells by activated macrophages and CD8+ cytotoxic T cells. The cytokine profile of T cells attracts the immune response in the periodontitis lesion [6]. In addition to immunoregulatory cytokines, it is now apparent that T-cell derived cytokines are directly involved in tissue destruction. *P. gingivalis* specific immune response is generated in adult periodontitis by T-cells. The immune response to self-antigens such as collagen type I, a major component of the periodontium, is also considered to be one of the pathogenic pathways. High titers of anti-collagen type I antibody are found in the sera and collagen type-specific T-cell clones can be identified in the inflamed gingival tissues of periodontitis patients [27]. T regulatory cells (TR cells) play a critical role in the generation and maintenance of tolerance in self-reactive T cells. A major function of suppressor T cells is to down-regulate the potentially pathogenic self reactive T cells without interfering with the response to foreign antigens. Killer T Cells (Cytotoxic T cells or CTL) are concerned with recognition and elimination of altered self-cells (e.g. Virus-infected or tumor cells)

B cells: Humoral Immunity is exhibited by B cells. On maturation, these cells leave bone marrow and express unique antigen binding receptors (Antibody molecules) on their surface. With the help of these molecules, B cells interact with antigens and differentiate into AB secreting plasma cells. Antibodies bind with antigen and execute its elimination from the body [3]. The proportion of B cells is larger than that of all T cells.

N.K. Cells (Natural Killer Cells): They are a subset of lymphocytes that kill infected cells and that have lost expression of class I MHC molecules. They secrete cytokines, mainly IFN-g, derived from bone marrow precursors and appear as large lymphocytes with numerous cytoplasmic granules. By surface phenotype and lineage, N K cells are distinct from T or B cells and they do not express immunoglobulins or TCRs.

Human immuno globulins: IgG - Gamma heavy chains, IgM - Mu heavy chains, IgA - Alpha heavy chains, IgD - Delta heavy chains, IgE - Epsilon heavy chains.

Antigen – Antibody Interaction: The reaction between an antigen and the homologous antibody is essentially a reaction between the epitope and paratope of the two molecules. The basic principles of antigen - antibody interaction are those of interactions between any bio molecular chemical reactions.⁷The strength of antigen -antibody reactions depend upon antibody affinity and avidity. Although Ag-Ab reactions are highly specific, in some case antibody elicited by one antigen can cross-react with an unrelated antigen. Such cross-

reactions occur if two different antigens share an identical epitope or if antibodies specific for one epitope also bind to an unrelated epitope possessing similar chemical properties.

Lock and Key Concept: The combining site of an antibody is located in the Fab portion of the molecule and is constructed from the hyper variable regions of the heavy and light chains. X-Ray crystallography studies of antigens and antibodies interacting show that the antigenic determinant nestles in a cleft formed by the combining site of the antibody. Thus, our concept of Ag-Ab reactions is one of a key (*i.e.* the Ag), which fits into a lock (*i.e.* the Ab). The bonds that hold the Ag in the antibody-combining site are all non-covalent in nature. These include hydrogen bonds, electrostatic bonds, Vander Waals forces and hydrophobic bonds. Multiple bonding between the Ag and the Ab ensures that the Ag will be bound tightly to the Ab. Since Ag-Ab reactions occur via non-covalent bonds, they are reversible by their nature.

Complement [3]: Complement (C) is an interacting network of about 30 membrane-associated cell receptors and soluble serum glycoproteins. The soluble components of the complement system were first observed to cause bacteriolysis and cytolysis in association with antibody (a “complement” of antibody), and later in the absence of antibody. These lytic effects are famous but represent only one function of complement. The complement system is a central component of inflammation that enables endothelium and leukocytes to recognize and bind foreign substances for which they lack receptors.

Complement promotes inflammation by generating the following:

- A vasoactive substance, termed *kinin-like*, C2a, which induces pain and increases vascular permeability and dilation.
- Molecules, termed *anaphylatoxins*, C3a and C5a, which produce anaphylaxis by inducing mast cell secretion.
- A chemotaxis, C5a, which attracts leukocytes and stimulates phagocyte secretion.
- An opsonin, iC3b, covalently bound to molecular aggregates, particles, or cells, which enables phagocytes to ingest them.
- C3 is the most important component of complement. It also is the predominant component, accounting for about one third of the total complement (1.6 mg/ml). A sequestered, internal thioester bond is the essential feature of C3, and it shares this feature with the related molecule, C4. Splitting of C3 forms C3a and C3b and exposes the internal thioester bond residing within the C3b fragment. Two main pathways result in the splitting of C3: the *alternative* and *classical* pathways. The outcome of C3b generation is dictated by the presence or absence of the regulators of complement activation. Both the alternative pathway and the classical pathway lead to inflammation and phagocytosis through an enzyme that is designated a *bound C3 convertase*.

Leukocyte functions [8]

Chemotaxis: Once the leukocyte enters the connective tissue, it must be able to locate and migrate to the site of insult. This is accomplished by *chemotaxis*, which depends on the leukocyte's ability to sense a chemical gradient across its cell body and migrate in the direction of increasing concentration

^{19, 31}. The phagocyte senses only a limited number of chemicals (chemotaxis) for which it has receptors and chemotaxis receptors.

Phagocytosis: Phagocytosis is the process by which cells ingest particles of a size visible to light microscopy. Neutrophils and monocytes/macrophages are the only cells efficient enough at phagocytosis to be considered “professional phagocytes.” Phagocytosis results in the eventual containment of a pathogen within a membrane-delimited structure, the *phagosome*. The immune system has evolved mechanisms of coating the pathogen with a few recognizable ligands, which enable the phagocyte to bind to and ingest the pathogen. This is referred to as *opsonization*. Once a microbe has been ingested, it may be killed. Phagocytes kill bacteria through two broad categories of killing mechanisms. One category is based on the reduction of oxygen and is referred to as “oxidative.” *Oxidative mechanisms* require (1) the presence of oxygen and (2) an oxidation-reduction potential, Eh, at or above -160 mV.

Transendothelial Migration: The directed movement of leukocytes from the blood into the local tissues is central to inflammation. Transendothelial migration is a selective interaction between leukocytes and endothelium that results in the leukocyte pushing its way between endothelial cells to exit the blood and enter the tissues. Defects in transendothelial migration are associated with aggressive periodontitis, reflecting the importance of this process in periodontal diseases. They constantly exit the blood, pass through lymphatics and secondary lymphoid organs, and re-enter the blood in a perpetual process known as *lymphocyte recirculation*. The blood contains only 2% of all lymphocytes at any given time, and lymphocytes are estimated to recirculate as much as 50 times a day.¹⁰ In a local inflammatory response, transendothelial migration occurs in the following sequential phases: rolling (step 1), an insult to local tissue (step 2), signaling the endothelium (step 3), increased rolling (step 4), signal for rolling arrest (step 5), strong adhesion (arrested rolling) (step 6), and the zipper phase (step 7).

Molecular biology

Antimicrobial peptides: These peptides have broad specificity with activity against gram-positive and gram-negative bacteria, as well as against yeast and some viruses. The β -defensins hBD1, hBD2, and hBD3 are found in oral and sulcular epithelium but not in junctional epithelia and are expressed in all human epithelial tissues tested to date^[11]. Alpha defensins are seen in junctional epithelium, which are produced by neutrophils passing through the epithelium even in health.

Toll like receptors (TLRs): These structures are referred to as pathogen-associated molecular patterns (bacterial lipopolysaccharide, peptidoglycan, lipoproteins). They transmit information through intracellular signaling pathways, resulting in activation of innate immune cells. The Toll-like receptor-mediated innate immune response is also critical for the development and direction of the adaptive immune system. Upon ligand binding, Toll-like receptor-mediated signaling activates signal transduction, leading to transcription of pro-inflammatory cytokines that initiate innate immune responses critical for the induction of adaptive immunity. The differential ability of oral bacterial

lipopolysaccharide to stimulate and signal through Toll-like receptors may induce host immune responses selectively.

Lipoxins: Lipoxins are generated during transcellular biosynthesis, which requires two cell types involving distinct lipoxygenases. Three main pathways of lipoxin synthesis have been identified. In the first pathway, in human mucosal tissues such as the gastrointestinal tract, the airways and the oral cavity, sequential oxygenation of arachidonic acid by 15-lipoxygenase and 5-lipoxygenase, followed by enzymatic hydrolysis, leads to the production of lipoxin A₄ and lipoxin B₄. In the second pathway, in blood vessels, 5-lipoxygenase biosynthesizes lipoxin A₄, and 12-lipoxygenase in platelets produces lipoxin B₄. Lipoxin A₄ regulates cellular functions through the activation of specific receptors (lipoxin A₄ receptor/formyl peptide receptor 2 and G protein-coupled receptor 32); these receptors are expressed by neutrophils and monocytes. A third synthetic pathway is triggered by aspirin. Aspirin promotes the acetylation of cyclooxygenase-2, leading to a change in cyclooxygenase-2 activity and in the chirality of the products, which are termed aspirin-triggered lipoxins.

Resolvins: Resolvins are lipid mediators that are induced endogenously during the resolution phase of inflammation. These lipid mediators are biosynthesized from the precursor essential ω -3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid derived from the diet. The two major groups of the resolvins family have distinct chemical structures: E-series, derived from eicosapentaenoic acid; and D-series, derived from docosahexaenoic acid. Production of resolvins E1 is increased in the plasma of individuals taking aspirin or eicosapentaenoic acid, resulting in the amelioration of the clinical signs of inflammation. Similarly, D-series resolvins have been shown to reduce inflammation by decreasing platelet-leukocyte adhesion, and aspirin-triggered docosahexaenoic acid conversion produces molecules with dual anti-inflammatory and pro-resolution functions.¹² Resolvins induce the hallmark functions of resolution of inflammation, including prevention of neutrophil penetration, phagocytosis of apoptotic neutrophils to clear the lesion and enhancing clearance of inflammation within the lesion to promote tissue regeneration.

Protectins: Protectins are also biosynthesized via a lipoxygenase-mediated pathway. This pathway converts docosahexaenoic acid into a 17S-hydroxyperoxide-containing intermediate that is rapidly taken up by leukocytes and converted into 10,17-Dihydroxydocosahexaenoic acid, known as protectin D1^[13] or neuroprotection^[14]. The name accounts for the protective actions observed in neural tissue and within the immune system. Both protectins reduce polymorphonuclear neutrophil transmigration through endothelial cells and enhance the clearance (efferocytosis) of apoptotic polymorphonuclear neutrophils by human macrophages.

Maresins: Macrophage mediators in resolving inflammation (maresins) were recently identified as primordial molecules produced by macrophages with homeostatic functions. Macrophage phagocytosis of apoptotic cells triggers the biosynthesis of resolvins E1, protectin D1, lipoxin A₄ and maresin-1. Conversion of docosahexaenoic acid into 14-hydroxy dihexaenoic acid was identified to occur via the 14-lipoxygenase pathway. Freshly prepared 14-H(p)

docosahexaenoic acid is rapidly converted by macrophages into bioactive products [15]. Maresin-1 effectively stimulates efferocytosis with human cells and also has regenerative functions.

Inflammatory mediators of the immune system

Connective tissue alteration [16]

Bacterial products [17]: 1. Degrade basement membrane and extracellular matrix proteins including collagen, proteoglycans, and glycoproteins. This would destroy periodontal connective tissue and facilitates bacterial invasion. 2. Interferes with tissue repair by inhibiting clot formation or lysing the fibrin matrix in periodontal lesions. 3. Activates latent host tissue collagenase which would enhance host-tissue enzyme mediated tissue destruction. 4. Inactivates proteins important in host defense.

Proteinases (Matrix MetalloProteinases) (MMPs): MMPs are any of the several enzymes that contain zinc and that digest specific extracellular matrix components, contributing to matrix equilibrium and structural integrity of the organism.

Elastase: Elastase degrades elastin, collagen and fibronectin. Elevated levels in GCF is associated with active periodontal attachment loss.[3]

CathepsinG: Cathepsin G is a bactericidal proteinase which also activates MMP-8. It is elevated in GCF in chronic periodontitis. [18]

Immunological Aspects of Periodontal Diseases

Periodontal health: There is some minimal inflammation with an associated flow of fluid into the healthy sulcus and the presence of some inflammatory cells in the tissues. T cell sensitization to plaque antigens is low. Serum antibodies to most oral bacteria are detected in healthy subjects.

Gingivitis: [19, 20, 21] It is a primary response to the bacteria in plaque. It includes a vascular response with increased fluid accumulation and inflammatory cell infiltration. The early response is mostly lymphocytic, represented by T cells, which is slightly higher.

Chronic periodontitis: [22, 23, 24, 25, 26, 27, 28, 29, 30] Increase in serum and crevicular fluid antibody specific to putative pathogens, including *P. gingivalis*, *A. actinomycetemcomitans*, *P. intermedia*, *E. corrodens*, *F. nucleatum*, and *C. rectus*, are evident. It involves alternative pathway activation of complement, with C3 and B cleavage in gingival fluids observed. Collagenase activity is associated with active periodontal destruction.[31] MMP-8 is elevated in chronic periodontitis. Studies reveal that collagenase activity is as much as sixfold greater than that of gingivitis in GCF in chronic periodontitis.

Refractory periodontitis [32, 33, 34, 35]: A higher level of IL-6 than stable patients have been reported. The presence of *P. gingivalis*, *E. corrodens*, or *A. actinomycetemcomitans* are correlated with elevated CGF IL-1 levels. CD4/Cd8 ratios are decreased in refractory periodontitis. *P. gingivalis*-lipopolysaccharide stimulation of monocytes cause a change in monocyte phenotype while increased IL-1 β and PGE₂ secretion in serum from refractory patients demonstrate increased IgG antibody to multiple periodontopathogens.

Aggressive periodontitis: [36] The prevalence of a humoral immune response to *A. actinomycetemcomitans* is elevated in patients with LAP. Numerous mechanisms of serum-mediated bacterial killing are proposed, including lysis by the membrane attack complex of complement and antimicrobial substances such as lysozyme. Generalized aggressive periodontitis is often characterized by defects in either neutrophils or monocytes. [37]

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