ORIGINAL RESEARCH PAPER
Volume-9 | Issue-5 | May-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF IMMUNOBIOLOGY IN PERIODONTAL DISEASE: CURRENT AND EMERGING PARADIGMS

Dental Science

Dr. Neelam Das* M.D.S., Assistant Professor, Department of Periodontics, Rama Dental College, Hospital & Research Centre, Kanpur (UP)- 208024*Corresponding Author

Dr. Janardhana Amaranath B.J M.D.S.,Principal, Department of Periodontics, Rama Dental College, Hospital & Research Centre, Kanpur (UP)- 208024

ABSTRACT

The patient's responses to periodontal infections are complex. There are many systems and much redundancy, withthe net effect that the host usually survives and the infection is controlled. However, there may be considerable loss ofthe alveolar bone and connective tissue supporting the teeth.Concepts have been presented based on recent developmentsin immunobiology, but this is only a current pictureof a rapidly-developing field. Many of the concepts presentedare already being challenged and will likely be changedwith more information. Our understanding of host responsesin periodontal disease is at a very early level. Thereare very few facts from which to develop cogent conceptsabout pathogenesis of periodontal disease and the role ofthe host, making it very difficult to make predictions todayas to which host factors may be useful in diagnosis.These, and as yet undescribed factorswhich play a key role in resolution of inflammation and healing, may be valuable indicators of periodontal disease in remission, or of subjects who are resistant to periodontal disease.Finally, due to an improved understanding of the pathogenesis of periodontal diseases, an additional approach to therapy with respect to modulation of host response has received attention.The future will see a range of host response modulators developed as adjunctive treatments for periodontitis. Therefore, it is very critical to understand the role of host response in periodontal diseases.

KEYWORDS

Host Response, Immunity,neutrophils, Periodontal Disease

INTRODUCTION

Periodontal diseases are complex bacteria-induced infections characterised by an inflammatory host response to plaque microbiota and their by-products.[1] Periodontitis is one of the major reasons for tooth loss in adults. However, local alteration and destruction of host tissues as a result of the microbial – host interactions may manifest as periodontal disease.[2] A disturbance in the equilibrium between bacteria and host, results in periodontal tissue destruction. As periodontal disease progresses, a series of events occur in bacterial plaque, gingival sulcus, junctional epithelium, connective tissue, and bone, due to alteration in tissue homeostasis. There is a gradual shift from gram-positive aerobic and facultative anaerobic flora to gram-negative anaerobic flora has been strongly associated with periodontal tissue breakdown.[3] Most of these microorganisms associated with periodontal disease have virulence factors capable of causing massive tissue destruction both directly, through tissue invasion and the production of harmful substances, or indirectly, by activation of host defence mechanisms, creating an inflammatory infiltrate of potent catabolic activity that can interfere with normal host defence mechanisms. In response to the aggression, host defence mechanisms activate innate and adaptive immune responses. The host response is mediated by the microbial interaction and inherent characteristics of the host, including genetic factors that vary among individuals. Host response to periodontal infection requires expression of a number of bioactive agents, including pro-inflammatory and anti-inflammatory cytokines, growth factors, and enzymes that are the result of the activation of multiple signalling pathways. Periodontal diseases provide a unique situation to study microbial-host interactions.

The major component of soft and hard tissue destruction associated with periodontal disease is the result of activation of the host's immuno-inflammatory response to the bacterial challenge**.** The immuno-inflammatory responses has been properly described as a **"double – edged sword"** and besides initiating destruction, it provides specific antibodies and polymorphonuclear neutrophils (PMNs) that dominant natural factors responsible for control of the bacterial challenge. The recent concept of etiopathogenesis of periodontal diseases states that of periodontal diseases encompasses three groups of factors which determine whether the periodontal disease will occur in: ***a sensitive host***, the presence of ***pathogenic species*** and ***absence of the so-called "beneficial bacteria"***. Host response not only plays a crucial role in maintaining homeostasis in periodontium during health but also influence the degree of periodontal tissue destruction, hence it is very important to have adequate knowledge on the role of host response in the pathogenesis of periodontal diseases, hence controlling of host response may prevent severe destruction of periodontal tissues by host modulation therapy.

Therefore, it is very critical to understand the role of host response in periodontal diseases. **First**, periodontal bacteria trigger inflammatory host responses which lead to tissue destruction. **Second**, data are accumulating from clinical and in vitro studies which suggest that the neutrophil/antibody/complement axis is critical for protection against periodontal disease. Abnormalities in this axis often lead to increased susceptibility to periodontal disease.

THESE INCLUDE:

1) Assessment of macrophage production of cytokines, which activate endothelial cell adhesion molecules necessary for the neutrophil to adhere to and pass through the vascular endothelium.
2) Measurement of the process of emigration by neutrophils to the site of inflammation.
3) Assessment of factors influencing opsonization and killing of bacteria by phagocytes. One or a combination of these measurements are likely to help identify susceptible hosts which will be useful in the management of periodontal diseases.

Third, "Periodontitis is a complex infection of bacterial origin in which multiple factors are implicated. It is characterised by an inflammatory host response against microorganisms of the bacterial plaque and their products". Measurement of factors which are responsible for healing such as the negative regulators of the inflammation including TGF-ß, interferon-7, IL-4, and interleukin-1 receptor antagonists may provide an assessment of periodontal disease in remission, or in the healing phase after treatment. These, and as yet undescribed factors which play a key role in resolution of inflammation and healing, may be valuable indicators of periodontal disease in remission, or of subjects who are resistant to periodontal disease. Finally, due to an improved understanding of the pathogenesis of periodontal diseases, an additional approach to therapy with respect to modulation of host response has received attention. Genetic factors which are responsible for increased susceptibility will provide powerful indicators for those in the population who are at high risk to develop severe periodontal disease. Host response modulators must be viewed as comprising part of the overall management strategy for patients with periodontitis. Periodontal disease is an unfortunate and distressing condition, and many patients are relieved to realize that multifaceted treatment strategies are possible, including, for example, root surface instrumentation, enzyme suppression and modification of local and systemic risk factors. Therefore, it is very critical to understand the role of host response in periodontal diseases. Hence, this review of literature was attempted to compile all the relevant scientific literature on role of host response in periodontal disease.

ROLE OF IMMUNITY IN PERIODONTAL DISEASE

Immunity is a state of having sufficient biological defences to avoid

infection, disease, or other unwanted biological invasion. The body either already possesses these defence mechanisms (non-specific or innate immunity) or may acquire it over a period of time due to exposure to harmful/ harmless organisms or substance (specific immunity).[4]

Classification of Immunity:-

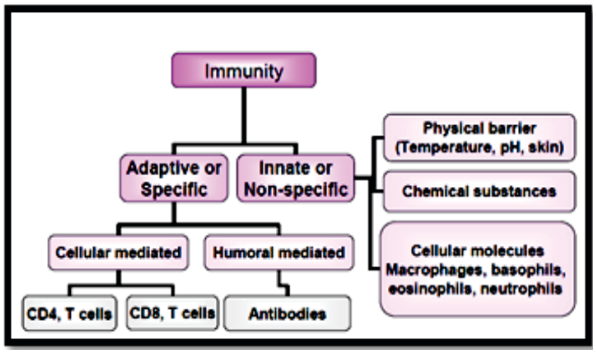

Figure-1. A diagrammatic representation of classification of immunity

The **Host Response** is also known as **Immune Response** and is defined as **"*The reaction of the immune system to injury resulting in inflammation it plays a central role in pathogenesis of periodontal disease*".**

In general, the host response functions in a protective capacity, preventing the local infection from progressing to a systemic, life-threatening infection. Immune response are categorized as:-

1) **Innate Immune Responses (Non- Specific)**
2) **Adaptive Immune Responses (Specific)**

Innate Immune Responses- may adapt with exposure to the same pathogen but subsides once the threat has been eliminated e.g.:- (monocytes, macrophages, neutrophils), which possess a number of inherently antimicrobial peptides and proteins that kill many different, rather than one specific, pathogen. It include the inflammatory response and do not involve immunological mechanism.

Adaptive Immune Responses- will increases after exposure to pathogen and usually maintains high levels for years and include immunological responses. Lymphocytes (T cells, B cells) are important in the fundamental form of specific adaptive immunity referred to as specific immune response.

Innate Immune Responses and Inflammation[5]

Innate immunity acts as a first line of defense against infections, and most potential pathogens are eliminated before they establish an overt infection. However, this emphasis in innate immunity targeted the ubiquitous nonspecific activities comprising an innate physiologic process called inflammation. The literature focused on the inflammatory response providing an orderly sequence of coordinated events devised to protect the host from infections and to minimize damage to host tissues. In periodontal health, a transudate fluid, reflecting the passage of serum or other body fluids through basement membranes, bathes the gingival sulcus. The vascular phase of inflammation affects the microcirculation, resulting in increased leakage of fluid from gingival capillary beds and the influx of polymorphonuclear leukocytes, creating a cell-rich inflammatory exudate. Production of this inflammatory exudate is a hallmark of the acute inflammatory response to provide a primary nonspecific defense. Host-response cells have been shown to contain a histamine, leukotrienes, heparin, serotonin and hyaluronic acid, as well as antimicrobial enzymes and factors. It further depicted that if these first defenses were unsuccessful, a chronic inflammatory response would ensue, involving many cells and biomolecules of the adaptive immune system.

The adaptive/ acquired immune system was separated into two branches:

1) **Humoral immunity**
2) **Cell –mediated immunity**

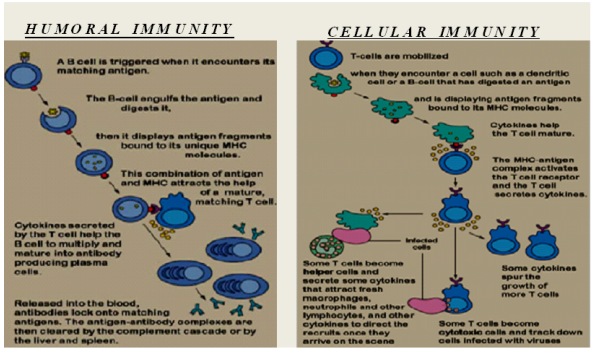

Figure-2. Activation of B-cells and T-cells

Cell-Mediated Immunity[6] includes a range of actions based upon the requirement for viable cells to be present to affect the immune outcomes. Cellular immunity evolved to support the notion that a primary cell type in this immunity pathway – the T-lymphocyte – was associated with two distinct types of immunologic functions: effector and regulatory. The effector functions included activities such as killing of virally infected cells and tumors. In contrast, the regulatory functions served to amplify or suppress the immune response through cytokines and/or receptor–ligand interactions of co-stimulatory molecules acting on other effector lymphocytes, including B- and T-cells.

The hallmark of **Humoral Immunity** is the production of antibodies, which are proteins produced by B-lymphocytes that are uniquely constructed to interact with the immune-stimulating antigens. The type of protective acquired immunity differs with different infectious agents. In general, protection mediated by humoral antibody (immunoglobulin) is effective against agents that exist extracellularly. In contrast, intracellular parasitic infections are principally resolved by cell mediated immune reactions. B-cells are derived from the bone marrow, which remains the major repository for B-lymphocyte stem cells throughout life.

The Immune Response:[7]

- The essence of the immune response is to production of antibody or cells that protect the host from injury by an invading pathogens.

A) Antigenicity and Immunogenicity.
B) Immunoglobulins and Antibodies.
C) Antibody- Antigen Reactions:

- The resultant antibody – antigen complex is an equilibrium reactions described by the equation: **Ag + Ab ↔ AgAb**

D) Humoral Vs Cellular Immune Responses
E) Activation Of The Immune System:

- There are several accessory molecules that play a role in T- cell activation.; the CD28 molecules, residing or the T- cell, and its complementary ligand B7 present on the target cells.
- The CD4+ mediated delayed type of hypersensitivity (DTH) responses differ from CD8+ mediated cytotoxic T- lymphocyte (CTL) response as indicated below:

Primary react	**Secondary reaction**	**In vivo effect**
TDTH cell + Ag →	Transcriptional activation → Proliferation lymphokine Release	Macrophage attraction and activation
TCTL cell Ag + Target →	Transcriptional activationn → Perforin Granyzymes	Target cell killing

F) Control of The Immune Responses:

Cells of Immunity and Inflammation[8]

1. Mast cells
2. Dermal dendrocytes (histocytes)
3. Peripheral dendritic cells
4. Neutrophils
5. Plasma cells
6. Monocytes/ Macrophages

a) T-CELLS
b) B-CELLS
c) NK-CELLS

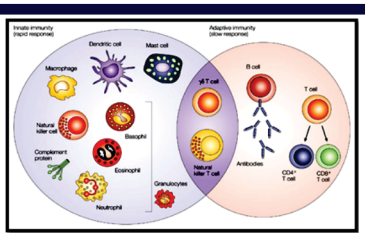

Figure - 3. Cells present in innate and adaptive immunity and few cells common in both.

Function of cells of Immune System:

CELLS	FUNCTIONS
Basophil	Receptor profile responds to bacterial and parasite infection.
Neutrophils	Phagocytic killing of microorganisms.
Monocyte	-Can differentiate into macrophages. -Function in phagocytosis and antigen processing and presentation.
Peripheral dendritic cell	Processing and antigen presentation.
Eosinophil	Antiparasitic and antihelminthic activity.
CD8+ cells	Scanning antigen & clonal expansion and filling of cell antigen presentation.
Mast cells	Anaphylactic effect: -Antigen recognition.
B cells	Binding soluble antigen, antigen processing and presentation, in inflammation, this may result in clonal expansion and antibody secretion.
NK-cells	Scanning cell antigens, target cell killing if KAR scans antigen, no killing if KIR scans antigen
CD4+ cells	Antigen presenting cells.

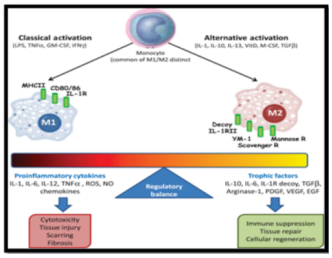

Figure. 4. Phenotypes of macrophages with varied stimuli and functional capacity that affect th characteristics of host responses.

Role of Complement System In Immunology [9]

The complement system refers to a series of proteins circulating in the blood and bathing the fluids surrounding tissues. It is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b9 membrane attack complex. Complement proteins circulate in the blood in an inactive form. Components of complement systems are proenzymes. Role of complement system is one of the most important antibacterial system in our body.

It occurs by 3 mechanisms:-

A.CLASSICAL PATHWAY.
B. ALTERNATE PATHWAY.
C. LECTIN PATHWAY.

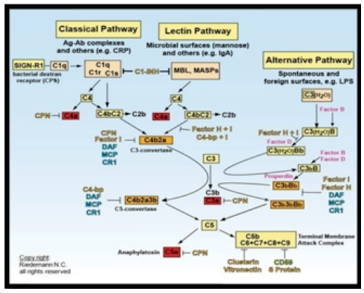

Figure-5. Complement reaction sequence

Transendothelial Migration [10]

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.

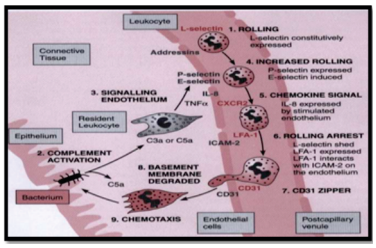

Figure- 6. Inflammation is a result of the interaction between complement, resident leukocytes, endothelium, and the recruited inflammatory leukocytes.

Leukocyte Functions [11]

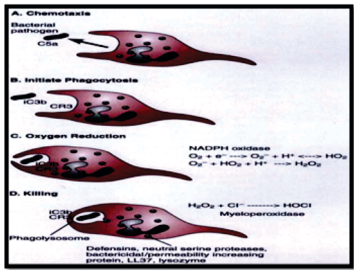

Figure- 7. After neutrophils exit the blood, they must kill the offending pathogens. This process consists of overlapping steps, which are illustrated in this diagram. A, Chemotaxis refers to directed motility that enables the leukocyte to locate its target. C5a is a chemotaxin, which may be generated by any target that activates complement. B, Phagocytosis also requires the interaction of receptors with a few ligands. The diagram illustrates the important interaction between the opsonin iC3b, which will coat an offending particle or cell, and the opsonic receptor CR3. C, Oxygen reduction requires the presence of oxygen and a certain redox potential, both of which can vary in the gingival crevice. The formation of several oxygen metabolites can kill some bacteria. D, Killing involves several processes. First, phagocytosis traps the microorganism in the stringent environment of the phagosome. Second, the phagosome and lysosomes (granules) fuse to form the phagolysosome. In this step, all the toxic compounds of the lysosome (e.g., defensins, neutral serine proteases) are dumped into the phagolysosome. Third, myeloperoxidase in the phagolysosome can convert hydrogen peroxide to hypochlorous acid.

Generation Of Acute Phase Signals:

Transendothelial migration- It is the selective interaction between leukocytes and endothelium that results in the leukocytes pushing its way between endothelial cells to exit the blood and enter the tissues.

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. This is a receptor mediated event that is initiated by chemotactic factors forming a concentration gradient that directs the approach of phagocytic cells.

Opsonization- It refers to the process of coating a particle with recognizable molecules to enable phagocytic ingestion. The two types of opsonins are complement metabolite (C3b) and immunoglobulin (IgG).

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." The

immune system has evolved mechanisms of coating the pathogen with a few recognizable ligands, which enable the phagocyte to bind and ingest the pathogen. This is referred to as opsonization. Bacteria within the phagosome and phagolysosome may be killed by oxidative or nonoxidative mechanisms.

Killing And Digestion- There are two killing mechanisms one is oxidative mechanism and is non-oxidative mechanism.

Antigen Processing And Presentation- The major histocompatibility complex (MHC) is a locus on the short arm of chromosome 6 that encodes a number of molecules, including MHC Classes I, II, and III molecules, which are involved with antigen uptake, processing, and presentation. All cells process and present self-derived antigens (intracellular antigens) in association with MHC Class I molecules. MHC Class I molecules are used to present intracellular antigens to CD8+T-cells and NK-cells. MHC Class III molecules include complement factors B, C2, and C4.

ETIOLOGY OF PERIODONTAL DISEASES

Periodontal diseases are infections that are caused by microorganisms that colonize the tooth surface at or below the gingival margin. The ecological relationships between the periodontal microbiota and its host by and large are benign in that damage to the supporting structures of the tooth is infrequent. Gingivitis, the initial reversible stage of Periodontal disease is associated with inflammation of gingival tissues without detectable evidence of clinical attachment or bone loss. [12]

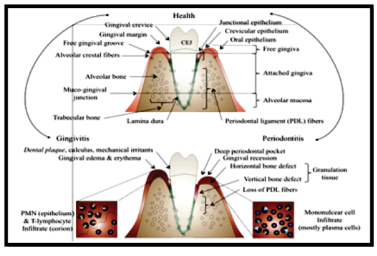

Figure-8. Gingivitis and Periodontitis

The hypothesis of periodontitis pathogenesis formulated by Page & Schroeder in 197613 stated that in response to subgingival pathogenic bacteria the host responds by an acute inflammatory response characterized by infiltration of neutrophils in gingiva, vasodilation and release of acute phase mediators. This is considered the initial lesion. It is now known that these early lesions (4-10 days after stimulation) are characterized by release of matrix degrading enzymes from leukocytes and fibroblasts. The established lesion that develops within 2-3 weeks is characterized by a mononuclear cell infiltrate predominated by B-lymphocytes and plasma cells, continued destruction of gingival extracellular matrix and a pool of pro-inflammatory cytokines and chemokines. The transition from the established lesion to periodontitis, characterized by loss of attachment, apical migration of attachment epithelium and loss of alveolar bone is not completely understood. Multiple host and biofilm factors are involved in this transition.

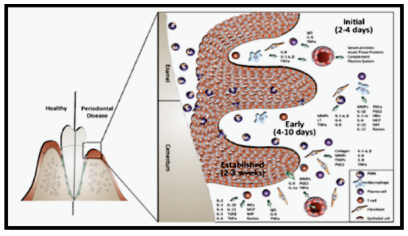

Figure- 9. Periodontal Tissue Destruction In Periodontitis.

Microbiological Etiology Of Periodontal Diseases

Dental Plaque As A Host Associated Biofilm[14]

Dental plaque is a bacterial biofilm which is a complex association of many different bacterial species together in a single environment. The plaque biofilm community is initially formed through bacterial interaction with the tooth, and then through physical and physiological interactions between different species within the microbial mass. Furthermore, the bacteria within the plaque biofilm are also influenced by host- mediated environmental factors. In this regard, Periodontal Health can be regarded as a state of balance in which the bacterial population co-exits with the host and no irreparable damage occurs to either the bacteria or the host. However, disruption of this balance may cause alterations in both the host and biofilm bacteria and result ultimately in destruction of periodontal tissues.

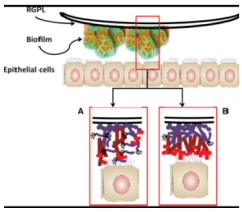

Figure.10. Considerations for multispecies biofilms of oral bacteria interacting with epithelial cells and potential for resulting differential characteristics of subsequent innate immune and/or inflammatory responses.

Development of Plaque As Biofilm[15]:

The process of plaque formation can be divided into several phases:

1. Formation of pellicle on the tooth surface
2. Initial adhesion and attachment of bacteria
3. Colonization and plaque maturation

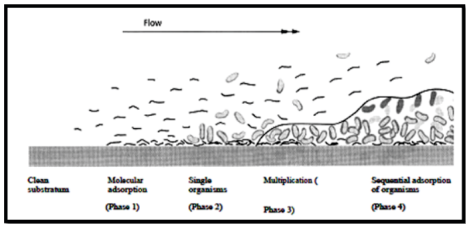

Figure – 11. Stages in the formation of a biofilm on a clean, hard and non-shedding surface following immersion into a fluid environment. Phase 1: Molecular adsorption to condition the biofilm formation. Phase 2: Bacterial adhesion by single organisms. Phase 3: Growth of extracellular matrix production and multiplication of the adhering bacteria. Phase 4: Sequential adsorption of further bacteria to form a more complex and mature biofilm. Adapted from Marshall (1992).

Impact Of Host Response In Periodontal Disease

Interaction Between Dental Plaque and Periodontal Tissues

Periodontal diseases are complex bacteria-induced infections characterised by an inflammatory host response to plaque microbiota and their by-products. Most of these microorganisms have virulence factors capable of causing massive tissue destruction both directly, through tissue invasion and the production of harmful substances, or indirectly, by activation of host response, creating an inflammatory infiltrate of potent catabolic activity that can interfere with normal host response. The host response is set up to eliminate the pathogens by the innate and adaptive immune responses. In health, the commensal bacteria and the host defense mechanisms are in a dynamic steady state. During periodontal disease progression, the dental bacterial plaque, junctional epithelium (JE), inflammatory cells, connective tissue, and bone all go through a series of changes. The tissue homeostasis is turned into tissue destruction and progression of periodontitis.

The Junctional Epithelium-Bacteria Interactions[16]

The first line of innate host defence in the periodontal region is the JE that hinders bacterial advancement into periodontal tissues.

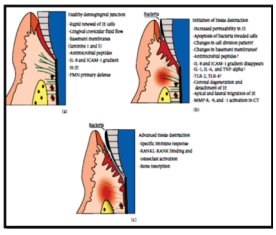

Figure- 12. (a) Healthy dentogingival junction is an active part of the innate periodontal defense. (b) The epithelium and connective tissue are affected at the initial phase of periodontal tissue destruction. (c) In periodontitis the epithelial barrier is broken, bacteria may invade the tissue (black spots), and connective tissue and bone are degraded. Junctional epithelium, dark red. Connective tissue and periodontal ligament fibers green, and bone yellow. Bacteria black, pocket

epithelium light gray. (a) Is a modified version of a figure from Pollanen et al.[17]

Connective Tissue Response To Bacterial Challenge

Bacteria at the gingival margin causes drastic changes in CT; vascular permeability and the amount of inflammatory cell infiltrate are increased. Fibroblast functions are altered; cell proliferation and collagen production are impaired and components of extracellular matrix are degraded.[18] This is thought to result from both host and bacteria-derived agents, such as lipopolysaccharides (LPSs), inflammatory cytokines, for example, IL-1beta, and TNF-alpha and to a lesser extent also by IL-17, growth factors and hormones[19] that activate leukocytes, fibroblasts, and epithelial cells leading to production of prostaglandins and MMPs and causing destruction of the CT.[20] Increased levels of MMPs and decreased amounts of their tissue inhibitors have been connected to the progression of periodontal disease [21] Although the immune response is primarily aimed to protect the host from the bacteria, it also seems to be strongly involved in tissue destruction in the periodontal region, Figure 12 (c).

Microbial Interactions With Oral Epithelium

The oral epithelium particularly the junctional and sulcular epithelia, represents a dynamic physical and chemical barrier against the pathologic properties of the microbial biofilm. Both host immune and bacterial factors are involved in the progression from healthy to diseased state in plaque biofilm, and in the oral cavity, gingival epithelial cells are one of the first host cell types that encounter colonizing bacteria. Epithelial tissue challenged by bacteria reacts by mobilizing their own antimicrobial mechanisms and by permitting cells of the innate and adaptive immune system to access the pathogens.[22] Cells of the junctional epithelium and resident leukocytes express antibacterial peptides including calprotectin α and β defensins,[23] cathelicidin, and IL-37 contributing to host defence and up regulating in tissues of patients with chronic periodontitis.

Current Understanding Of Microbial Interactions With The Host In Periodontal Diseases

I) Microbiologic Aspects Of The Host- Microbial Interaction

The interaction of the microorganism with the host determines the course and extent of the resulting disease. Microorganisms may exert pathogenic effects directly by causing tissue destruction itself or indirectly by stimulating and modulating the host response. Research on virulence factors has focused on the properties of bacteria related to the destruction of host tissues. These bacterial properties can be broadly categorized as those resulting directly in degradation of host tissues and those causing the release of biologic mediators from host tissue cells that lead to host tissue destruction.

II) Immunologic Aspects Of The Microbial Interaction With The Host

Periodontal disease is dependent on bacteria, and bacteria may directly interact with the host tissues in mediating tissue destruction. In addition, many tissue changes associated with periodontal diseases appear to be well-orchestrated responses, suggesting the influence of host regulation.

Among the orchestrated responses are the antimicrobial activities by acute inflammatory cells (neutrophils) and the adaptive activities brought about by monocytes/macrophages and lymphocytes. Adaptive responses include the epithelial alterations, angiogenesis, episodic remodeling of the underlying of hard and soft connective tissues, and antigen- specific immune responses. Remodeling of the connective tissues appears to be episodic and occurs in cycles of destruction and reconstruction. Excessive destruction or inadequate reconstruction can result in periodontal disease. In this paradigm, periodontal disease represents a well-regulated response to protect bacterial infection directed by the inflammatory cells of the host immune system.

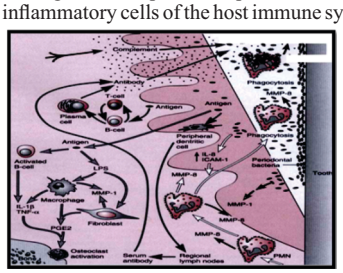

Figure-13. Schematic illustration of key processes of the host bacterial interaction in periodontal diseases.

HOST DEFENCE PROCESSES[24]

Innate reactions include the inflammatory response and do not involve immunological mechanisms. Adaptive reactions that include immunological responses tend to be more effective as the host response is specifically "tailored" to the offending pathogens.

The Role of Inflammatory Response In Periodontal Diseases

Various inflammatory mediators play a crucial role in acute and chronic inflammation of periodontal tissue. These include a range of interacting molecules like the Cytokine system, Proteinases, Proteinase Activators, Thrombin, Histamine, Prostaglandins, Leukotrienes, Tissue and Blood Factors such as Hageman's Factor, Complement and Clotting Factors. These mediators lead to the initiation and eventually termination of an inflammatory response to insult. These are present in inflamed gingiva and gingival crevicular fluid from diseased sites in high concentrations and their concentration typically decrease following successful periodontal therapy.

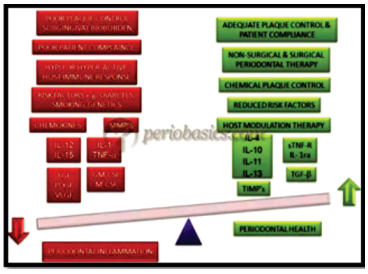

Figure-14. Balance between various factors and inflammatory mediators favouring periodontal health and disease.

Osteo-Immunology in Periodontal Diseases

Nowadays, it has been clearly demonstrated that increases in RANKL, mRNA and protein levels in periodontal tissues stimulate the differentiation of monocyte-macrophage precursor cells into osteoclasts, and the maturation and survival of the osteoclast, leading to alveolar bone loss. [25]

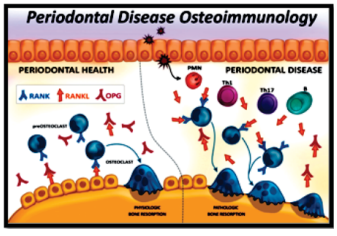

Figure- 15. Periodontal disease osteoimmunology

In this review, during inflammatory response characteristic of periodontitis, proinflammatory cytokines associated with T-helper 1 and T-helper 17 cell phenotypes, such as interleukin-1β, interleukin-6, interleukin-17, interferon-γ, and tumor necrosis factor-α, can stimulate periodontal osteoblasts to express membrane-bound RANKL.[26] In addition to osteoblasts, RANKL is expressed by a number of other cell types, mainly T-helper 17 lymphocytes.[27]

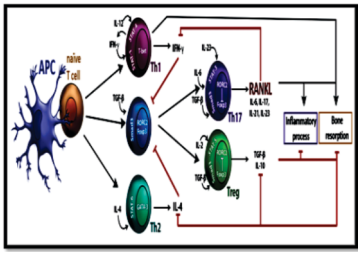

Figure- 16. Osteoclastogenesis and bone resorption induction through synthesizing interleukin-17 and RANKL

Induction Of The Immune Response In Periodontal Health And In Various Periodontal Diseases[28,29]

Immune Response in Periodontal Health:

To understand the periodontal immune response in gingivitis and periodontitis let us first try and understand immune response in periodontal health. The periodontium is considered healthy in the absence of inflammation. Usually we have subclinical inflammation.

One of the most important parts of periodontium that is central place for host immune response is the dentogingival unit. It is adaptation of the oral mucosa to tooth surface that comprises of epithelial and connective tissue components. ***The epithelium is divided into three functional compartments – Gingival, Sulcular, and Junctional Epithelium.*** The connective tissue is divided into superficial and deep compartments. Out of these, Junctional Epithelium plays most important role in periodontal health and disease states. In healthy state gingival tissue contains low number of leukocytes primarily classified as lymphocytes.

A substantial amount of literature has detailed the levels of inflammatory mediators in healthy and inflamed periodontal tissues. Some of them are summarized here:-

I) In clinically healthy gingival tissues, inflammatory cytokines are present in low quantities, suggesting cytokines are also prominent factors mediating normal tissue homeostasis.
II) Low levels of prostaglandin E_2 (PGE_2) have been found at sites free of periodontal inflammation as compared to inflamed site where there levels are high. Prostaglandin E_2 (PGE_2) is considered as marker of inflammation.
III) Low or no IL-1β is detected in tissue extracts from healthy sites, whereas its levels are clearly detectable in inflamed gingival sites.
IV) Levels of IL-8 have been found to be increased at healthy sites as compared to sites with periodontitis. IL-8 is a potent migratory signal for neutrophils to the site of ingress of bacterial products.
V) On examination of subjects with healthy gingiva and subjects with periodontitis it has been found that, less numbers of cells containing TGF-β1 are found in healthy gingival.

Immune Response in Gingivitis:

As explained in the previous sections, gingivitis starts with the accumulation and ingress of bacteria and their products through oral sulcular epithelium. Primary response to this is associated with the release of chemical mediators from junctional epithelium which causes recruitment of polymorphonuclear cells in that area. Now, various chemical mediators are secreted by immunocompetent cells during the host bacterial interactions. Gingival crevicular fluid has been used as an important source of analysis of various enzymes and inflammatory mediators. One experimental gingivitis study showed that the gingivitis was associated with a significant 2.6 fold increase in interleukin-1β (IL-β), a 3.1 fold increase in IL-1α and a significant decrease in multiple chemokines as well as MMPs-1,3 and 13.

Immune Response in Chronic Periodontitis:

Chronic periodontitis is characterized by slow progression of the disease. Various microbiological and immunological investigations have been done to analyse the mediators in immunological response. In one investigation IL-1β,TNF-α,IL-2,IFN-γ,IL-4 and IL-10 important mediators in the initiation and progression of periodontal diseases, within inflamed gingival tissues and serum samples from patients with severe chronic periodontitis were investigated. Results showed that serum samples showed insignificant relation with active disease but levels of IL-1β, TNF-α, IL-2 and IFN-γ and, especially their high ratios to IL-4 and IL-10 found in inflamed tissue biopsies, were closely associated with periodontal disease severity.

Immune Response in Aggressive Periodontitis:

The aggressive periodontal diseases are characterized by relatively severe and rapid destruction of periodontal tissue. Aggressive periodontitis is characterized by functional abnormalities of host cells, particularly neutrophils that possess a hyperactivated or primed phenotype. The functional consequences of neutrophil priming include defective chemotaxis, phagocytic abnormalities, and elevated pro-inflammatory activity including increased oxidative stress and secretion of inflammatory mediators. As already stated, impaired polymorphonuclear neutrophil (PMN) functions are generally considered to be related to the onset of generalized aggressive periodontitis.

MOLECULAR BIOLOGY OF THE HOST-MICROBE INTERACTION IN PERIODONTAL DISEASES

The molecular biology of the host-parasite relationship from a cellular signalling perspective specific to pathogen-associated lipopolysaccharide (LPS). Host response to periodontal infection requires expression of a number of bioactive agents, including proinflammatory and anti-inflammatory cytokines, growth factors, and enzymes that are the result of the activation of multiple signalling pathways. This activation of intracellular signalling may initiate exclusively as an innate immune response associated with PRR-mediated sensing of MAMPs. However, the focuses on host-microbe interaction, we will emphasize the direct recognition of MAMPs by cells participating in the immune response and the molecular mechanisms activated downstream of this recognition.[30]

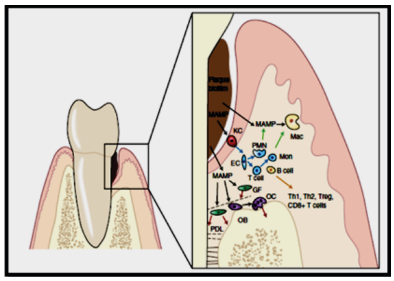

Figure-17. Microbial-associated molecular pattern (MAMP) from microorganisms in the dental biofilm activate inflammatory responses in periodontal tissues. Biologic mediators will either affect neighboring cells (blue arrows) by inducing the expression of other mediators (e.g., RANKL) or by triggering chemotaxis (green arrows). Direct damage to periodontal tissues may also result after MAMPs stimulation (red arrows), such as metalloproteinase secretion by gingival and periodontal ligament fibroblasts.

Role of Toll- Like Receptors In Innate- Immune Response

Among the most important families of pathogen-associated pathogen associated molecular patterns are the toll-like receptors (TLRs), which recognize, with selectivity, a large number of varied and complex pathogen-associated molecular patterns. Toll-like receptor provide rapid first- line innate defense against infection, and also act as mediators between the innate and adaptive immune responses. Interestingly, within the periodontal tissues, the expression of various TLRs appears to be increased in severe disease states.[31]

Cell Signalling Pathways and The Expression Of Biologically-Active Mediators In The Innate Immune Response

Once MAMPs are recognized by the appropriate PRRs, a signal is initiated within the cell. This signal is transduced through the cytoplasm and nucleus more commonly by sequential posttranslational modification (e.g., phosphorylation) of a cascade of kinases that are constitutively expressed and ultimately will determine the cell response to the MAMPs detected. These can lead to the activation of different cell signalling pathways and subsequent modulation of the host response.[32]

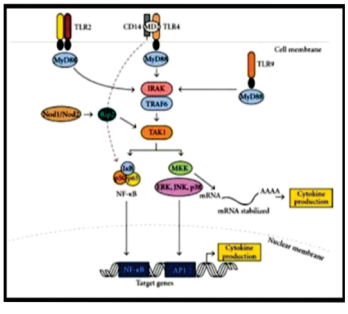

Figure-18. Pattern recognition receptors (PRRs) and innate immune signalling.

CLINICAL RELEVANCE OF THE HOST RESPONSE OF PERIODONTITIS

The host response in periodontal disease can be considered in many ways, i.e. as the processes that render a subject susceptible to disease or as the pathology of the lesions or as the processes involved in the acute and chronic inflammatory lesion of periodontitis.

If we consider all of these categories of "host Response" we are then set a difficult task in determining which ones are truly of **"*Clinical Relevance*", *defined as "those features which if present change our clinical decision-making or patient management".*** Clearly, there are different forms of periodontitis, different rates of susceptibility to these forms, different responses, different genetics and risk factors at play and different modifiers of these diseases. All of these factors are based on variations or modifications of the host response and are thus

pertinent to this current review.

Concept of Host Susceptibility

For many years, it was noted that some individuals might be very susceptible and will develop aggressive forms of periodontitis at a relatively young age, while others might be resistant and will never develop periodontitis. [33] The susceptibility of the host is determined in part by genetic factors but can be influenced by environmental/ behavioral factors such as smoking, stress, and viral infections.

Host Susceptibility To Gingivitis

Gingivitis susceptibility and indeed resistance are now accepted entities, but we do not know how these relate to periodontitis. The clinical relevance of this is that certain patients will develop gingivitis more readily. Another possibility is that gingivitis may be the normal host response that holds the effects of microbial plaque in check and does not permit further destruction of the periodontal tissues. To further complicate matters, both gingivitis and periodontitis could be independent of each other both pathologically and with respect to risk factors.[34]

Host Susceptibility To Periodontitis

Despite its explanatory power for periodontal disease pathogenesis, the concept of keystone pathogens and pathobionts leaves a number of questions unanswered. The breakdown of tissue homeostasis leading to the blooming of inflammophilic pathobionts may not necessarily come from within the microbial community, that is, by the action of keystone pathogens. The host–microbe homeostasis can also be disrupted by congenital or acquired host immunodeficiencies or immunoregulatory defects, systemic diseases such as diabetes, obesity, environmental factors, such as smoking, diet, and stress, and epigenetic modifications in response to environmental changes, which alone or in combination can contribute to unfavorable tipping of the homeostatic balance.[35]

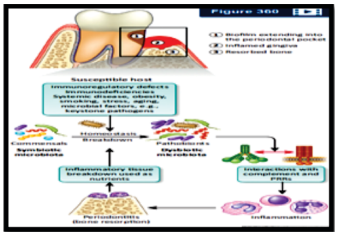

Figure-19. Polymicrobial synergy and dysbiosis in susceptible hosts causes periodontitis. It should be noted that host susceptibility might not simply be a determinant of the transition from a symbiotic to a dysbiotic microbiota but it may also underlie the predisposition of the host to develop inflammation sufficient to cause irreversible tissue damage.

Influence Of Genetic Factors On Host Response To Periodontal Infection

Periodontitis is a multi-factorial disease for which several risk and susceptibility factors are proposed in the natural history of periodontitis.36 Genetics is considered a susceptibility factor in relation to periodontitis. Periodontal research has greatly expanded to elucidate the role of genetics in periodontal disease states. Consequently, there has been great interest in identifying allelic variants of genes that can be used to assess disease risk for periodontal diseases. Reports of genetic polymorphisms associated with periodontal disease are continuously increasing.

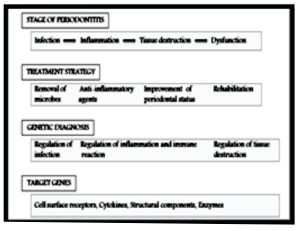

Figure-20. Relationship between genetic diagnosis and target genes at various stages of periodontitis and their treatment strategy.

Risk Factors That May Modify The Innate And Adaptive Immune Responses In Periodontal Diseases

Modifying factors can be defined as those factors that alter the nature or course of the inflammatory lesion. In this context, these factors do not cause the disease but rather modify the chronic inflammatory response that is characterized by a vascular response, a cellular response and the simultaneous presence of destruction and repair. The nature of this chronic inflammation is mediated by the nature of the innate and adaptive immune responses and the cytokine and inflammatory mediator networks. Modifying factors are largely systemic and can influence the manifestation and/or progression of the disease. Factors that may influence either the innate immune response, or indeed the nature of the adaptive immune response, also influence the nature of the inflammatory response in the gingival tissues.[37]

Host Response Therapeutics For Periodontal Diseases

Resolution of Inflammation

Resolution of inflammation is an active process that results in a return to homeostasis, and is mediated by specific molecules including a class of endogenous, pro-resolving lipid mediators, the lipoxins, resolvins, and protectins".[38] These molecules are actively synthesized during the resolution phases of acute inflammation, they are anti-inflammatory, and they inhibit neutrophil infiltration. They are also chemo-attractants but do not cause inflammation. The new idea to be explored here is the shift from anti-inflammation to resolution as a means of controlling periodontitis.

Concept Behind Host Modulation[39,40]

Host modulation is a therapy that is targeted at the modulation of host response. As already stated, the result of host bacterial interaction is the release of various inflammatory mediators that cause tissue destruction. Using various therapeutic agents that can down-regulate or inhibit the production, activation or biological function of these mediators is the basic concept of host modulation therapy. Our present understanding of the pathogenesis of periodontal disease has led to the development of host modulation as a treatment strategy that can be used in addition to conventional treatment approaches. This therapy acts on the host part of host microbial interaction. Host response modulation refers to the down regulating destructive aspects of the host response so that; the deleterious effects of various inflammatory mediators on host tissues are reduced.

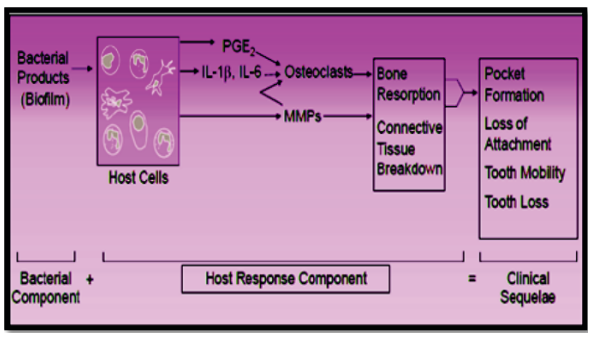

Figure- 21. Periodontal breakdown cascade

The concept of host modulation was first introduced by ***Williams (1990) and Golub et al (1992).*** This shift in paradigm of concentration on host response has led to the development of Host Modulatory Therapies (HMT) which could improve therapeutic outcomes, slow the progression of disease, allow for more predictable management of patients, and possibly even work as preventive agents against the development of periodontitis.

Where To Give Host Modulation Therapy?

As we know that bacterial challenge is the main etiological factor in the development and progression of periodontitis. Many studies have clearly demonstrated that reduction in microbial load leads to reduction in inflammation in periodontal tissues. But, many patients do not respond appropriately to this therapy and the periodontal tissue breakdown continues. Periodontal diseases are multifactorial diseases.

HOST MODULATION THERAPEUTIC AGENTS

To understand the host modulation therapeutic agents, let us first try to understand the steps where the agents modulate the host response.

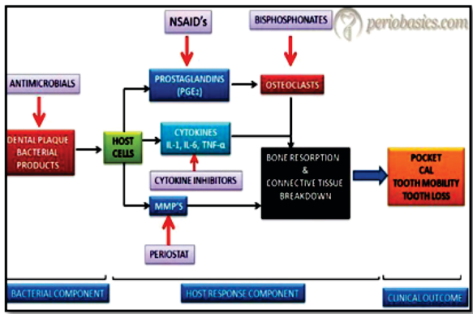

Figure- 22. Diagram showing various host modulation therapeutics agents

Classification Of Host Modulation Therapeutics (salvi And Lang, 2005) [41]

1. Modulation of Immune and Inflammatory responses

i. Modulation of cytokine inhibition
ii. Eg-Blockade of receptors for IL-1, Tumor necrosis factor (TNF) and Advanced glycation end products (AGEs)

2. Modulation of Arachidonic acid metabolites

i. Nonsteroidal anti-inflammatory drugs (NSAIDs) and triclosan
ii. Lipoxixns and resolvins

3. Modulation of bone remodelling

I. Bisphosphonates
ii. Anti- inflammatory agents
iii. Chemically modified teracyclines
iv. Hormone replacement therapy for post- menopause women

4. Modulation of Matrix Metallo Proteinase (MMP) activities

i. Eg- Tissue inhibitor metallo proteinases (TIMPs) and sub antimicrobial dose of tetracyclines (SDD).

5. Modulation of Nitric oxide synthase (NOS) activity

i. Eg- Mercapto ethylguanide.

6. Modulation of cell signalling pathways in periodontal disease

7. Host Modulation by promoting periodontal regeneration

Emerging Host Modulatory Therapies [42]

I) Disruption of cell signaling pathways for treating periodontitis

Strategies for preventing cell activation seek to inhibit the intracellular transduction of signals produced when ligands bind to their membrane receptors. Signal transduction pathways are activated not only by cytokines, but also by other factors, such as bacterial proteins, lipopolysaccharide, or environmental stress. Inhibition of signal transduction pathways by cytokine suppressive anti-inflammatory drugs (CSAIDs) would be expected to abolish both cell activation by cytokines or other stimuli and the production of pro-inflammatory cytokines.

II) Kinase inhibitors:

Kinase inhibitors are potential new targets for periodontal therapies. Kinases are intracellular molecules involved in signal transduction during inflammation. Following binding of a ligand to a cell-surface receptor, numerous cytoplasmic kinases are activated that then modulate the activity of transcription factors, and thus regulate gene expression.

Two types of kinases can be targeted: ***Mitogen-activated protein kinases and tyrosine kinases***. A number of oral drugs that target these complexes have been tested in animal models of periodontitis and found to reduce inflammatory cytokine production and osteoclast formation, and thus protect against inflammatory mediated alveolar bone loss.

***Mitogen-activated protein kinase* (MAPK) *pathway*:** MAPKs are divided into three families: The extracellular signal-regulated kinases (ERK1/2); C-Jun N-terminal kinases (JNKs); and p38. They control the synthesis of compounds, including chemokines, metalloproteinases, and Pgs.

1) JNK inhibitor: It has been suggested that JNK signaling pathway contributes to inflammatory responses in mammals and play a role in T-cell differentiation and the cellular apoptosis pathway.The specific JNK inhibitor (SP600125) not only diminishes the production of TNF-α, interferon-γ, IL-6, COX-2, and MMP, and also decreases joint destruction in the adjuvant arthritis model.

2) ERK1/2 inhibitor: The specific ERK1/2 inhibitor, blocks T-lymphocyte activation and proliferation and induces modest anti-inflammatory effects in several experimental models.

3) p38 MAPK: Activation of p38 within cells induces synthesis of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8, either via direct activation of gene transcription or via messenger ribonucleic acid (mRNA) stabilization.In addition, p38 MAPK controls the synthesis of other compounds, including chemokines, metalloproteinases, and PGs. The role for p38 MAPK in the various stages of inflammation has prompted the production of several imidazole compounds capable of inhibiting p38 (SB203580, VX-745, and others).

III) Disruption of the RANKL/RANK/ osteoprotegerin axis: RANKL mediates a signal for osteoclastogenesis through RANK on pre-osteoclast cells. The RANKL/RANK interaction is responsible for differentiation and maturation of osteoclast precursor cells to activate osteoclasts. Osteoprotegerin acts as a decoy receptor, expressed by osteoblastic cells, which binds to RANKL and inhibits osteoclast development.

IV) The NF-κB pathway inhibitors: It controls the expression of many mediators involved in periodontal inflammation, such as IL-1, IL-6, TNF-α, collagenases, adhesion molecules, and chemokines. The NF-κB family includes p50, p52, and p65. *In vitro* studies have established that *Porphyromonas gingivalis* and other periopathogenic bacteria can activate NF-κB in periodontal tissues. Bacterial lipopolysaccharide and the pro-inflammatory cytokines IL-1 and TNF, all present in large quantities in periodontal diseased tissues, can also activate NF-κB.

Host Modulation And Comprehensive Periodontal Management

This concept is extremely important considering the chronic nature of the disease. However, controlling the bacteria that cause periodontal infections remains a central focus of effective periodontal treatment. Understanding the importance of the host response and the impact of risk factors now allows clinicians to provide complementary treatment strategies simultaneously for their patients.

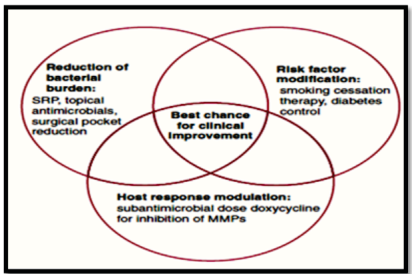

Figure-23. Complementary treatment strategies in periodontitis.

FUTURE PERSPECTIVES

Advancements in adjunctive host modulation therapy could help the cause related periodontal therapy. Greater awareness of the role of the host response in periodontal disease will further improve the understanding of the severity and therapy of periodontal infections. Finally, the recognition of the beneficial activity of several groups of commensal species might open new strategies for treating periodontal disease, for example, using probiotics or microbial replacement therapy.[43] The potential future use of Cytokines in treatment of periodontal disease seems promising, due to their potent biological effects in very low concentrations. For example, IL- 4 can control the macrophage response to LPS, and block parts of the cytokine cascade evoked by macrophage-derived cytokines. One approach is to use cytokine inhibitors or receptor-blockers to diminished tissue response to tissue-destructive cytokines. Another approach to this goal is the control of the intracellular transduction mechanisms leading to cytokine gene expression. [44] The importance of the **Selectins** in the inflammatory process is now widely accepted. They have been found to be expressed on endothelial cells in sites of infection and inflammation in several animal models of disease such as acute lung

injury, extrinsic asthma, and ischemie reperfusion injury in the heart. The evidence that supports the importance of the selectins in humans is the recent discovery of a leukocyte adhesion deficiency type 2.[45] The use of **Growth Factors** in periodontal regeneration seems promising. The growth factors can be used to control specific events in early and late phases of the periodontal wound repair.

New Developments [46]

A new family of surface active agents, **Pluronic Polyols**, have an effect on tissue repair and wound healing. The pluronic polyols have a positive effect on fibroblast growth in culture as well as enhancing burn wound healing. The pluronic polyols appear to modulate regeneration by topical application and can be used as a vehicle for topical use of other growth factors.

CONCLUSION

There has been substantial progress in our understanding of the molecular mechanisms of host–bacteria interactions that result in the clinical presentation and outcomes of destructive periodontitis. We have learned how the armamentarium of the innate immune, inflammatory and adaptive immune responses 'team' in unique ways, depending upon host, microbial and environmental controls, to maintain or re-establish homeostasis. However, these inherent 'good guys' can double-cross the control points for a regulated response, resulting in dysregulated chronic inflammation and collateral damage of the periodontium. As importantly, the next era in the immunobiology of periodontal disease will need to engage more sophisticated experimental designs for clinical studies to enable robust translation of basic biologic processes that are in action early in the transition from health to disease. Periodontal therapy in the 21st century should not only involve a high standard of clinical treatment and monitoring, but should also focus on patient involvement and improving the patient experience. The future will see a range of host response modulators developed as adjunctive treatments for periodontitis. The further development of these agents will permit dentists to treat specific aspects of the underlying biochemical basis for periodontal disease. Therefore, it is very critical to understand the role of host response in periodontal diseases.

ACKNOWLEDGMENT: The author declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS: The authors contributed to update all relevant information to formulate the design, drafted the manuscript review. The authors gave final approval and agree to be accountable for all aspects of the work.

FINANCIAL SUPPORT AND SPONSORSHIP: Nil.

CONFLICTS OF INTEREST: There are no conflicts of interest.

REFERENCES

[1] Chickanna R, Prabhuji M, Nagarjuna M. Host- bacterial interplay in periodontal disease. J Int Clin Dent Res Organ 2015; 7 (1): 44-50.
[2] Albandar JM. Periodontal diseases in North America. Periodontol 2000 2002; 29: 31-69.
[3] Carison BM. Academy report- Informational report. Modulation of the host response in periodontal therapy. J periodontol 2002; 73(5): 460-70.
[4] Harshmohan. Textbook of Pathology. 5th edition.
[5] Rose F Louis, Mealey L Brian, Robert J. Genco. Periodontics medicine, surgery and implants. D Water Cohen: Mosby inc; 2004.
[6] Singh A, Mehdi AA, Srivastava RN, Verma NS. Immunoregulation of bone remodelling. Int J Crit Illn Inj Sci. 2012; 2: 75–81.
[7] Immunology of periodontal diseases. Periobasic.com.
[8] Robbins and Cotran. Pathologic Basis of Disease. 7th edition.
[9] Nisengard and Newman. Oral microbiology and immunology. 2nd ed. W.B saunders company.
[10] Grant, Stern, and listgartan. Periodontics. 6th edition.
[11] Newman MG, Takei H, Klokkevold PR, Carranza FA. Carranza Clinical Periodontology. 11th ed.USA: Elsevier Health Sciences; 2015.
[12] Offenbacher S. Periodontal diseases: pathogenesis. Annals of periodontology / the American Academy of Periodontology. 1996; 1(1): 821–78.
[13] Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. Lab Invest 1976; 34(3): 235–49.
[14] Moore WEC. Microbiology of periodontal disease. J Periodontal Res 1987; 22: 335-49.
[15] Prosser JI. Quorum sensing in biofilm. In: Newman H.N. and Wilson M eds. Dental Plaque Revisited. Cardiff: Bioline. 1999; 79-88 p.
[16] Salonen JI. "Proliferative potential of the attached cells of human junctional epithelium." J Periodontal Res 1994; 29(1): 41-45.
[17] Pollanen MT, Salonen JI, Uitto VJ. "Structure and function of the tooth-epithelial interface in health and disease." Periodontol 2000 2003; 31: 12–31.
[18] Ren L, Leung WK, Darveau RP, Jin L. "The expression profile of lipopolysaccharide-binding protein, membrane- bound CD14, and toll-like receptors 2 and 4 in chronic periodontitis." J Periodontol 2005; 76(11): 1950–59.
[19] Hakkinen L, Larjava H. "Characterization of fibroblast clones from periodontal granulation tissue in vitro." J Dent Res 1992; 71(12): 1901–7.
[20] Beklen A, Ainola M, Hukkanen M, Gurgan C, Sorsa T, Konttinen YT. "MMPs, IL-1, and TNF are regulated by IL- 17 in periodontitis." J Dent Res. 2007; 86 (4): 347–51.
[21] Reynolds JJ, Meikle MC. "Mechanisms of connective tissue matrix destruction in periodontitis." Periodontol 2000 1997; 14: 144–57.
[22] Dereka XE, Tosios KI, Chrysomali E, Angelopoulou E. Factor XIIIa + dendritic cells and S-100 protein + Langerhans' cells in adult periodontitis. J Periodontal Res 2004; 39: 447-52.
[23] Vankeerberghen A, Nuyen H, Dierickx K, Quirynen M, Cassiman JJ, Cuppens H. Differential induction of human β-defensins expression by periodontal commensals and pathogens in periodontal pocket epithelial cells. J Periodontol 2005; 76: 1293-303.
[24] Martínez AB, Corcuera MM, Noronha S, Paula M, Ilundain CB, Trapero JC. Host defence mechanisms against bacterial aggression in periodontal disease: Basic mechanisms. Med Oral Patol Oral Cir Bucal 2009; 14(12): 680-5.
[25] Crotti T, Smith MD, Hirsch R, Soukoulis S, Weedon H, Capone M et al. Receptor activator NF kappa B ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. J Periodontal Res 2003; 38: 380-7.
[26] Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol 2008; 79: 1585-91.
[27] Rodan GA, Martin TJ. Therapeutic approaches to bone diseases. Science 2000; 289: 1508-14.
[28] Sorsa T, Mantyla P, Tervahartiala T, Pussinen PJ, Gamonal J, Hernandez M. MMP activation in diagnostics of periodontitis and systemic inflammation. J Clin Periodontol 2011; 38: 817-9.
[29] Cardoso CR, Garlet GP, Moreira AP, Júnior WM, Rossi MA, Silva JS. Characterization of CD4+CD25+ natural regulatory T cells in the inflammatory infiltrate of human chronic periodontitis. J Leukoc Biol 2008; 84(3): 11-8.
[30] Beutler B. Toll- like receptors: how they work and what they do. Curr Opin Hematol 2012; 169: 87- 88.
[31] Franchi L, Warner N, Viani K, Nunez G. Function of Nod-like receptors in microbial recognition and host defence. Immunol Rev 2009; 227: 106-28.
[32] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124: 783-801.
[33] Kinane DF, Hart TC. Genes and gene polymorphisms associated with periodontal disease. Crit Rev Oral Biol Med 2003; 14: 430–49.
[34] Genco RJ, Ho AW, Kopman J, Grossi SG, Dunford RG, Tedesco LA. Models to evaluate the role of stress in periodontal disease. Ann Periodontol 1998; 3: 288–302.
[35] Laine ML. Genetic susceptibility to periodontitis. Periodontol 2000 2012; 58: 37–68.
[36] Hart TC, Marazita ML, Wright JT. The impact of molecular genetics on oral health paradigms. Crit Rev Oral Biol Med 2000; 11: 26-56.
[37] Nassar H, Kantarci A, Van Dyke TE. Diabetic periodontitis: a model for activated innate immunity and impaired resolution of inflammation. Periodontol 2000 2006; 43: 233–44.
[38] Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving mediators and pathways. Annu Rev Immnol 2007; 25: 101-37.
[39] Host modulation in periodontics. http://periobasics.com/.html.
[40] Host response therapeutics for periodontal diseases. http://periobasics.com/.html.
[41] Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. J Clin Periodontol 2005; 32(6): 108-29.
[42] Readdy MS, Jeffcoat MK, Richardson RC. Assesment of adjunctive flurbiprofen therapy in root- form implant healing with digital substraction radiography. J Oral Implantol 1990; 16: 272-6.
[43] Kono Y, Ogawa T, Beagley KW. Immunopathology of periodontal disease: Studies with interleukins which mediate both Immunoglobulin synthesis and inflammation in diseased gingiva. In: Hamada S, Holt SC, McGhee JR, eds. Periodontal Disease: Pathogens and Host Immune Responses. Tokyo: Quintessence Publishing Co., Ltd.; 2016; 209-22.
[44] Male D, Champion B, Cooke A, Owen M. Advanced Immunology. Philadelphia: J Lippincott Company; 1991.
[45] Wakelin D. Immunity to parasites. 2nd edn. Cambridge University Press;2015.
[46] Thomas E, Dyke V, Mary AL, Lior S. The role of the host response in periodontal disease progression: implications for future treatment strategies. J Periodontol 1993; 64: 792-806.