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THE PERIODONTAL GAME OF THRONES: HOST VERSUS MICROBES

Dental Science

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ABSTRACT

95% of the Indian population suffers from periodontal disease. The periodontal disease is caused by invasion of microbes on the tooth surface which leads to the activation of the host immune response. This **periodontal war** is thus a battle of two kingdoms – The Host and the **Microbes** and is a never-ending process. Over the years pathogens have developed resistance against the immune responses of the host giving them an edge to flourish and cause more widespread and virulent disease. This review article focuses on understanding the changes in **host immune system** following microbial insult which leads to periodontal destruction. The etiology of periodontitis and role of **keystone pathogen** has also been highlighted.

KEYWORDS

The periodontal war Microbes Host immune System Keystone pathogen

India suffers lot of disparities in terms of oral health care and 95% of the Indian population suffers from periodontal disease.[1] Periodontitis is a manifestation of complex interaction between the host and microbes- the periodontal war.

The periodontal War is a battle of two kingdoms – The Host and the Microbes. The host's strategy is its immune response and the microbial strategy is three faceted – Adhesion, Sustenance and Evasion.

"Don't fear the enemy who attacks you, fear the friend who hugs you"

Earlier microbes were thought to be primary aggressors that governed the host – pathogen interaction resulting in disease. However, research has shown there exists symbiosis between the host and microbes (commensals). It is under the influence of certain pathogens identified as "keystone pathogens" that these friends turn foe and start harming the host.[2]

KINGDOM 1: MICROBES
THE INDESTRUCTIBLE BIOFILM

" The action is in the interaction" – Douglas Conant

The first step towards periodontal disease is formation of biofilm whose foundation is the co-aggregation between periodontopathogens. The biofilm is formed with first the action of early colonizers followed by bridging species to finally presence of late colonizers. The attachment of early colonizers that comprises of *Streptococcus* and *Actinomyces* species is a crucial step. By forming channels within the biofilm, they provide the nutrition and environment that is conducive for the growth of anaerobic bacteria and late colonizers.[3,4] The Fusobacteria are the bridging species which can interact with both gram negative and gram-positive bacteria thereby forming a pivotal link between primary and secondary dental plaque colonization. The coaggregation between *P. gingivalis* and *F. nucleatum* is an important one. *F. nucleatum* supports *P.gingivalis* growth by providing a capnophilic environment when growing in an oxygenated and CO_2 depleted environment.[5,6]

P. gingivalis is usually detected with *T.denticola* in subgingival plaque – a cooperative synergistic growth relationship may exist between them.[7] Apart from the red complex recent studies have shown association of a gram positive anaerobe *F.alocis* with periodontitis.[8,9] The interactions between various oral species through receptor-ligand binding, nutritional support, protection against the environmental stresses and coaggregation in biofilm is the topmost strategy employed by microbes to win this host- microbe periodontal war.[10]

KINGDOM 2: THE HOST

"The supreme art of war is to subdue the enemy without fighting" – Sun Tzu

As the warning bell of biofilm formation strikes a series of events are triggered within the host. The advanced pattern recognition receptors(PRR) called the toll like receptors (TLR) are adept at recognizing various components of the microbes like capsule, lipopolysaccharides etc.[11,12] Their activation triggers the first line of defence –innate immunity. Neutrophils are first cells to get recruited at the site of attack and gradually the complement system of body comes into play. The activated complement leads to release of C3 protein. It is responsible for release of opsonins and its further activation forms a membrane attack complex(MAC) against the pathogens.[13,14] This coordination between TLRs and complement is referred as the TLR-complement crosstalk.[15] Innate response occupies a crucial position both in the host's defence as well as the microbe's strategic planning to evade the host.[16,17,18]

Initial priming of dendritic cells (antigen presenting cells, APC) occurs by interaction of microbial antigen with the major histocompatibility complex(MHC). Once stimulated mature dendritic cells control the immune response with the cytokines-initiated release of T effector cells.[19] In the presence of IL-2 and IL-4 T-helper cell differentiates into a Th2 cell while the T box (T-bet) differentiates into a Th1 cell involved in macrophage activation, phagocytosis, complement fixation and opsonization that are protective against intracellular bacteria.[20] Th1 response under the influence of IL-12, IL-2 and IFN-γ enhances the phagocytic activity of both neutrophils and macrophages, while Th2 response under the influence of IL-4 cytokines has non- protective antibody function. The T-helper cell also differentiates into a Th17 cell which is pro-inflammatory.[21,22] Macrophages play a crucial role in innate and adaptive immune response. M1 phenotype is pro-inflammatory, M2 is anti- inflammatory while M3 exhibits plasticity and switches from M1<->M2 depending on stimuli.[5,23,24](Figure 1)

GINGIVAL EPITHELIUM

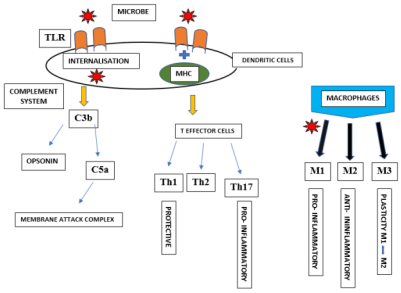

FIGURE 1: Changes in host immune response following microbial insult

THE BATTLEFIELD: HOST-MICROBIAL WAR

LINING THE ENEMY TERRITORY:

The ability of pathogen to adhere to the host and initiate colonization is important as only after the pathogen has attached to the host it can initiate the disease. *P.gingivalis* has multiple strategies to enhance continued colonization of host tissues. Its fimbriae possess capability to attach to various host cells with integrin acting as a receptor causing upregulation of new polypeptides that favour *P.gingivalis* colonization. The proteases specifically R-gingipains can disrupt integrin-fibronectin interaction in gingival fibroblasts aiding in its translocation within the cells. [25,26]

T. denticola with the help of collagen binding proteins, major sheath protein(msp) and other surface molecules binds to an array of host-cell receptors and surfaces.[27] The tight adherance (tad locus) of *A.actinomycetemcomitans* has been linked to its colonization process. Other bacteria in the biofilm colonize the host by their own adhesins or by their interaction with other microbes like Fap2, galactose-inhibitable adhesin of *F.nucleatum* is involved in its coaggregation with *P.gingivalis* and further its colonization within the host.[28,29]

PATHOGENS FLOURISH IN THE ENEMY HOST KINGDOM:

To initiate disease the major requirement of microbes is to sustain itself within the host and compete for physiologic requirements which is possible by their virulence. The two major sustenins include- Proteases and Metabolic end products.[30] The gingipains and exopeptidase of *P.gingivalis* are degradative to a number of host proteins enabling it to compete effectively in periodontal habitat for its metabolism, growth and replication. Dentilisin the protease of *T.denticola* contributes to providing not only energy for bacterial growth but also an environment conducive for growth of anaerobic bacteria.[31] Periodontopathogens have also adopted strategies to acquire "heme" from the host that provides energy for their growth.[32,33] The metabolic end products of microbes like volatile sulfur compounds of *P.gingivalis* have been shown to be cytotoxic to the host cells which further enable these putative pathogens to adjust to stresses and sustain within the changing environment of the periodontium.

HOST RETALIATION AND PATHOGEN SIDE-STEPPING:

To thrive in the host, it is imperative to evade the attack strategies (immune response) of the host. Evasion strategies include alteration in recruitment of neutrophils, upregulation of pro-inflammatory cytokines specifically IL-6, altering the cytokine network and bypassing the complement system by an array of proteases.[34,35] Evasion is primarily achieved by modifying the innate host response. *F.nucleatum* can modify the killing capability of neutrophils and increase the disintegrin and MMP 8 in host impacting the innate host response .[36] The main role is of *P.gingivalis* (keystone pathogen) which along with other coaggregating species provides resistance to the pathogenic against host providing an environment for the pathogens to flourish and disease progression occurs.

AFTER EFFECTS:
PERIODONTAL DESTRUCTION

The periodontal destruction initiated by microbes is primarily propagated by host response. The interaction between periodontal inflammation and persistent bacterial infection up-regulates the expression and activity of neutral proteinases which contributes to the progressive breakdown of periodontal supporting tissue.[37]

The periodontopathogens particularly *P.gingivalis* possess the ability to affect macrophage programming by increasing M1 thereby inducing a hyperinflammatory response in the host.[38]

Enhanced expression of RANK in precursor of osteoclast and the MMPs occurs with the upregulation of Th17 by periodontopathogens.[39,40] Various molecules are released from leukocytes and fibroblasts as soon as immunoinflammatory processes begin and an imbalance between the level of activated tissue-destroying MMPs and their endogenous inhibitors occur. MMPs are released and activated during periodontal inflammation by proinflammatory cytokines, like TNF-α, interleukin-1β, reactive oxygen species, and proteases derived from the subgingival biofilm and the host.[41] MMP-8 is mainly associated with periodontal collagen destruction. MMP-13 upregulation has been involved in periodontal bone loss.[42] Higher mRNA expression levels of MMP/TIMP ratios for MMP-1, -2 and -9, as well as RANKL/ osteoprotegerin ratio, have been reported in gingival tissue from chronic and aggressive periodontitis patients.[43,44]

With the destruction of connective tissue attachment and the junctional epithelium the inflammatory infiltrate migrates apically. Osteoclast activation occurs through direct and indirect mechanisms involving RANK, RANKL and Osteoprotegerin modulation leading to bone loss. In presence of periodontopathogens, CD4+ T cells show increased RANKL expression. As the destructive pattern continues, subsequent increase in microbial density propagates the periodontal lesion. The shift to a more anaerobic flora leads to a more destructive and chronic host response.[45](Figure 2)

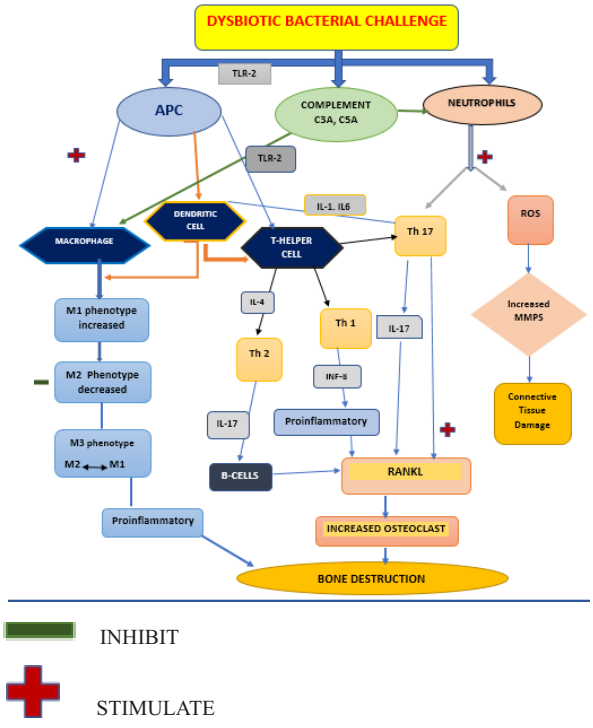

FIGURE 2: Sequence of events leading to Periodontal destruction

THE ETIOLOGY OF PERIODONTITIS:

From the non specific plaque hypothesis(1950s) by Macdonald et al to the Polymicrobial synergy and dybiosis(PSD) model by Hajishengallis (2012) we have come a long way in understanding the microbial etiology of periodontitis. (Figure 3)

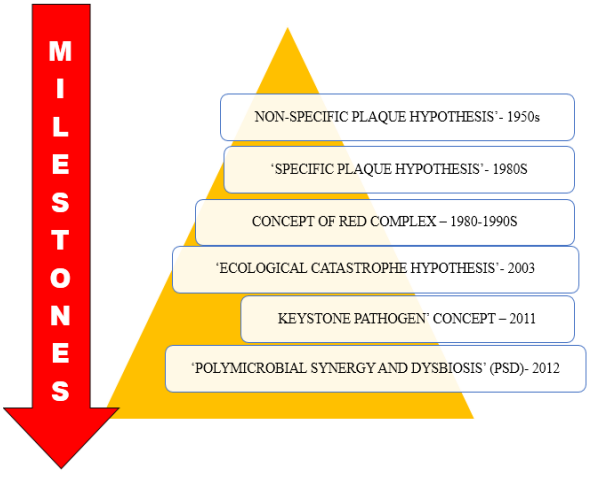

FIGURE 3: Milestones achieved in Etiology of Periodontitis'

The current hypothesis focuses on low number of keystone pathogens (*eg. P.gingivalis*) causing high abundance of commensal oral flora. Subsequently commensals turn to accessory pathogens (*eg S.gordonii)* which aid the keystones in converting other commensals into pathobionts (*eg T.denticola*). This causes a dysbiosis in the otherwise symbiotic relationship between the host and commensals. The PSD model states that dysbiosis causes the polymicrobial load to act

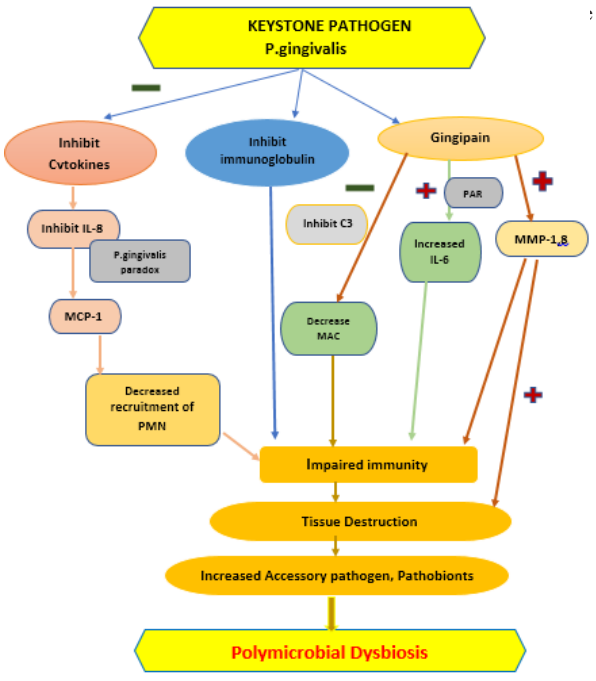

FIGURE 4: Role of Keystone Pathogen

INHIBIT

STIMULATE

SELF-DRAFTED

TREATMENT STRATEGIES:

The treatment aspect is perhaps the trickiest part of periodontitis. Being polymicrobial and multifactorial it is influenced by the environmental and also by genetic and epigenetic factors. Few therapies used include host modulation therapy [49], photodynamic therapy and administering substances like hydrogen peroxide to inhibit the growth of more virulent anaerobic microbes. Recent research has focused on formulation of vaccines to combat periodontitis.[50] However, focusing on a single pathogen does not give good results and better treatment strategies need to be developed.

CONCLUSION:

"Know your opponent and you will never lose, know yourself and you will always win" – Sun Tzu.

The host-microbial war is never ending. Over the years pathogens have developed resistance against the immune responses of the host giving them an edge to flourish and cause more widespread and virulent disease. Our knowledge of the microbial assault is still incomplete and insufficient in finding a permanent cure for periodontitis. Future research should be to employ strategies that target polymicrobial load as a whole instead of a single organism to combat the disease in a better and more effective way.

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