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Host bacterial interactions in periodontal disease: Review article

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Abstract
Bacteria constitute an important part of our environment .Indeed life without bacteria would be impossible. If we take about bacteria in context of periodontal disease, these microorganisms exert their effects directly by causing tissue destruction or indirectly by stimulating or modulating the host--tissue response. The pathogenesis of periodontal disease involves a complex interplay b/w bacterial pathogen and the host tissue. Recent investigations have revealed that not all strains of specific microbial species are equal in their capacity to cause disease and not all hosts are equal in their susceptibility.

Keywords: Host tissue, periodontal disease, bacterial pathogen

Introduction
Bacteria constitute an important part of our environment .Indeed life without bacteria would be impossible. If we take about bacteria in context of periodontal disease, these microorganisms exert their effects directly by causing tissue destruction or indirectly by stimulating or modulating the host-tissue response. The interactions of microorganisms with the host determine the course and extent of the disease [1].
Host response is a protective capacity preventing local infection from progressing to a systemic life threatening infection.

Host defence system of oral cavity [2]
A striking difference between the mouth and the other habitats of digestive tract is the presence of teeth. These teeth enable an accumulation of large number of microorganisms. The defense system of oral cavity can be.
1. Non-specific host defense system
2. Specific host defense system

Evasion Mechanisms
Various mechanisms have been proposed by which the bacteria of plaque might avoid or neutralize the host response. These mechanisms are
- Antigenic variations
- Immunological indifferences
- Immune suppression
- Antigen masking protease production
- Unfavorable environmental conditions
- Miscellaneous

Antigenic variation [3]
Gibbons *et al* 1975 Surface of oral streptococci undergo some continuous or subtle changes in their antigenic makeup to avoid antibodies.
Same strategy has been followed by Neisseria an obligate pathogenic bacteria to persist at the site of infection.

Immunological indifferences
Foo and Lee et al. 1972; proposed that the host cells respond less well to the some antigen
Because
- Either these bacteria share antigen with the same host.
- They have surface antigen masked by the adsorbed molecules from host secretions e.g. saliva

Bacteria could also evade the host response by production of capsules or slimy layer to mask surface receptors.

Protease production [4]
- **Killian *et al*. 1986**

Some bacteria may inactivate the host defense by production of proteases. IgA can inhibit adherence of bacteria to the tissue surface and many bacteria produce IgA specific protease and inhibit this action of sIgA.

- **Slot and Genco *et al* 1984**

Proposed that the various bacteria also produce proteases against IgM, IgA and IgG.

Immune suppression [4]
Various members of plaque flora e.g. *Veillonella* spp., *A. actinomycetemcomitans*, *Fusobacterium*, spirochetes have immune suppressive properties and could depress immune response sufficiently to allow other autocanthous bacteria to grow.

Unfavorable environment
E.g. Bactericidal properties of lactoferrin against *S. mutans* are abolished under anaerobic conditions.
Lysis of bacteria cell by Lysozyme protease system is less effective at neutral ph as compared to acidic ph.

Miscellaneous
Some bacteria suppress the activity of the PMN's or lymphocytes e.g. A.a produce leukotoxins and cytolethal distending toxins. *F. nucleatum* have been shown to induce apoptosis in lymphocytes.

Bacterial adherence to the periodontal environment [5]
Bacterial adherence represents a virulence factor (Def: virulence factor is the property of the microorganism that enables it to cause a disease.).
The surfaces which are available for attachment to the microorganism include root/tooth, tissue or preexisting plaque mass.
The bacteria which initially colonize the oral cavity get attached to the pellicle or saliva coated tooth surface.

Adhesion of bacteria [6]
A. actinomycetemcomitans and *P. gingivalis* get attached to the tissue /tooth surface through fimbriae.
Fimbriae also provide mode of adherence for co aggregation e.g. adherence of *A. viscosus* through fimbriae to polysaccharide receptors of cells of *S. sanguis*.

Adhesion of bacteria
P. gingivalis
The carboxyl- terminal region of fimbrillin is responsible for this binding.
There are two types of fimbriae structures on the cell surface of *P. gingivalis* i.e.
1. 41kD major fimbriae protein
2. 67 kD minor fimbriae protein

Through these fimbriae *P. gingivalis* also get attached to the fibroblasts and epithelial cell surface.
P. gingivalis has also the ability to bind to the commansal bacteria i.e. *S. gordonii* through 35kD fimbriae associated molecules.

Aggregatibacter actinomycetemcomitans
It follows fimbrial and non- fimbrial adherence mechanism.

Fimbrial Adherence Mechanism: freshly isolated A. a contain fimbriae on their structure and these are lost over long periods of sub culturing. Fimbriated strains attach 3-4 times better to hydroxyapatite than non fimbriated variants. Inoue *et al* has suggested that the major fimbrial structure of A. a. is 6.5 kD peptide also referred as Flp fimbrial low molecular weight protein.

Non-Fimbrial Adherence mechanism: Outer membrane protein of A.a. contain extracellular matrix adhesion protein A (EmaA) which act as direct mediator of adhesion of A.a to collagen.

Host tissue invasion [7]
- Both gram (+)ve and gram(-)ve bacteria including rods, cocci, filaments and spirochetes have been observed in gingival connective tissue and in the proximity to the alveolar bone.
- Primary mode of invasion: Bacteria may enter the host tissue through the ulceration in the epithelium of gingival sulcus or pocket.
- Direct invasion: Another mean of invasion may be direct penetration of bacteria into host cells both in connective tissue and in epithelium. e.g. *A. actinomycetemcomitans, P. gingivalis, F. nucleatum and T. denticola* can invade host tissue cells directly.
- Both A.a. and P. g follow *Ruffling Mechanism* while *F. nucleatum* follows zipping mechanism.

Connective tissue alterations: Tissue destruction in periodontitis [8]
Various mediators which are produced as a part of host-bacterial response and cause tissue destruction includes
1. Proteases(MMP's)
2. Cytokines (IL-1, IL-6, TNFα)
3. Prostaglandins(PGE_2)

Prostaglandins [9]
Prostaglandins are arachdonic acid metabolites generated by cyclooxigenase (Cox-1 and Cox-2).The primary cells responsible for the production of PGE_2
a) Fibroblasts
b) Macrophages.

PGE_2 causes
1. Induction of MMP'S
2. Induction of osteoclastic bone resorption.

Cytokines [10]
Three pro-inflammatory cytokines have a central role in the periodontal tissue destruction.

IL-1
Two active forms are found IL-1α and IL-1β encoded by

separate genes and once called as osteoclast activating factors. IL-1 is produced by macrophages, monocytes, osteoblasts and epithelial cells.
They promote bone resorption by osteoclast proliferation, differentiation and activation and inhibit bone formation.

TNF-α

It shares many biologic activities with IL-1 but they are less potent.

IL-6

Mainly participate in bone remodeling.
So pro-inflammatory effects of IL-1, IL-6, INF-γ and TNF-α includes

1. Stimulation of endothelial cells to express selectin that facilitates recruitment of leukocytes.
2. Activation of macrophages IL-1 production.
3. Induction of PGE_2 by macrophage and gingival fibroblasts.
4. Induce production of proteases (MMP's) in mesenchymal cells which contributes in connective tissue destruction.

Proteases [11]

MMP's are considered as primary proteinases involved in periodontal destruction by degradation of extracellular matrix molecules.
MMP's are basically a family of Proteolytic enzymes found in neutrophils, macrophages, fibroblasts, epithelial cells, osteoblasts and Osteoclasts that degrade extracellular matrix molecules i.e. collagen, gelatin and elastin.

- **MMP-8 and MMP-1 are both collagenase**

MMP-8 released from infiltrating neutrophils where as MMP-1 are expressed by resident cells i.e. fibroblasts, macrophages/monocytes and epithelial cells.
Collagenases are elevated in tissue and GCF associate with periodontitis. (Ingman *et al*. 1996)

- MMP's are secreted in latent or inactivated form
- MMP activation by Proteolytic cleavage of portion of latent enzyme by chymotrypsin like protease by T. denticola or neutrophils cathapsin-G
- MMP inactivation α macroglobulin found in serum and GCF and tissue inhibitors of MMP's

Connective tissue alterations: healing process in periodontitis [12]

- Regeneration is replacement of lost tissues with new identical tissue that function the same as original tissue.
- Repair is replacement of one lost tissue by another tissue such as fiberous connective tissue which may not function the same as the tissue replaced.
- After trauma surgical injury healing is initiated as a part of *immediate and acute inflammatory response*. Periodontal repair take place in 3 overlapping phases

1. Inflammation shutdown
2. Angiogenesis
3. Fibro genesis

Anti-inflammatory signals are generated by leukocytes i.e.

1. interleukin 1 receptor antagonist(IL-1ra) and
2. transforming growth factor β (TGF- β)

Other cytokine that produce anti-inflammatory responses are IL-4, IL-10 and IL-11.

Healing Process in Periodontitis [13]

IL-1α and IL-1β are indirectly involved in inducing *fibroblast proliferation* and *collagen synthesis* by stimulating PGE_2 or by release of platelet derived growth factor(PDGF) and transforming growth factor *β (TGF- β)*

- Platelet derived growth factor (PDGF) is found in 5 isoforms a-e. It activates fibroblast and osteoblast resulting in induction of protein synthesi.
- Source: endothelium, vascular smooth muscles and macrophages.
- Transforming growth factor *β (*TGF- β) is a multifunctional peptide that stimulates osteoblast, fibroblasts and inhibits osteoclast and immune cells. Receptors of transforming growth factor β are found in almost all the cells.
- INF-γ inhibits osteoclast differentiation and activation directly as well as indirectly by inhibition of IL-1, and TNF-α induced osteoclast activation.
- Interleukin 1 receptor antagonist (IL-1ra) is also effective in blocking IL-1 and TNF- α induced osteoclast activation.
- Insulin like growth factor -1 (IGF-1) help in inducing osteoblast growth differentiation and synthesis of collagen [14, 15, 16].

Conclusion

- The pathogenesis of periodontal disease involves a complex interplay b/w bacterial pathogen and the host tissue.
- Recent investigations have revealed that not all strains of specific microbial species are equal in their capacity to cause disease and not all hosts are equal in their susceptibility.

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