HOST
MODULATION
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• **HOST**: An organism from which a parasite obtains its nourishment or in the transplantation of tissue “the individual who receives the graft”.

• **MODULATION**: “the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment.” (Taber’s medical dictionary, 2004)
HOST MODULATION

(HOST RESPONSE MODULATION)

- Modifying or modulating destructive or damaging aspects in the periodontal tissues as a result of chronic challenge presented by the sub gingival bacterial plaque.
• Concept of host modulation first introduced to dentistry by:– (WILLIAMS AND GOLUB et al.)

• “There are compelling data from the studies in animal and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of periodontitis.
• In 1992, Golub and colleagues discussed “Host modulation with tetracyclines and their chemically modified analogues”.

• Newer agents that have the potential to be of benefit in periodontal treatment include anti-cytokine drugs (used in rheumatoid arthritis), soluble cytokine blockers and lipoxins
One systemic medication has been licensed as a host response modulation for the treatment of periodontal disease, and that is sub microbial dose doxycycline.
HISTORICAL
PROSPECTIVE
HIPPOCRATES - first dental healers

- describing a malady of loose teeth and bleeding gums.

In Rome, Celsius (30 BC)

- recommended vinegar as a remedy for gingival disorders, first documented attempt at managing the disease with chemotherapeutics.

Riggs (1881)

- introduced his techniques for the treatment of periodontal disease termed RIGG’S disease.

Younger and Hutchins on

- surgical treatment of periodontal inflammation by pocket obliteration.

C.M. Carr

- developed scalers for the removal of sub gingival deposits and for planning of root surfaces --- most aspects of modern periodontics actually started.
In 1960’s, it was recognised that systemic disorders often play an important role in the etiology of certain periodontal diseases.

Theorise about the pathogenesis of periodontitis have evolved from a purely plaque associated disease to more recent hypothesis, placing considerable emphasis on the host response to the bacteria.

The first surgeon report on oral health in America published in 2000 has recognised the importance of dental health in overall general health and well being of a patient.
Recent research findings indicate possible associations between chronic oral infections such as periodontitis and systemic disorders such as diabetes, heart and lung disease, stroke and adverse pregnancy outcomes.

Along with these findings and the emergence of discipline of periodontal medicine, there have been many developments in therapeutic approaches to the management of periodontitis.
HOST RESPONSE AND POTENTIAL TARGETS FOR HOST MODULATION
In 1985, focus on bacterial-host interactions.

Bacterial pathogens initiate the periodontal inflammation. The host response to these pathogens is equally, if not more, important in mediating CT breakdown including bone loss.

MMPs & changes in the osteoclastic activity driven by cytokines and prostanoids cause most of the tissue destruction in the periodontium.

This shift in paradigms, with the focus on the host response, - development of host modulatory therapies.
Assessment: Role of the Host Response in PDL Pathogenesis

1. Sub gingival plaque bacteria microbial subs (LPS, M.peptides, B.Ag)
2. Diffuse junctional epithelium into ging CT
3. DGJ indicates prior vulnerability to b.attack
4. Ep, CT stimulated to produce inflammatory mediators – inflammatory response in tissues
5. G vessels dilates – permeable to fluids & cells
6. Defense cells (PMNs) migrate - kill plaque bacteria
B cell entering tissue

Commited Lymphoctes return to site of infection

Host immune – inflammatory response established

B cells -transformed to plasma cells – ABs - phagocytosis & B killing killing

Gingivitis develop
Disease Resistant - primary defense mechanisms control the infection & chronic inflammation (i.e. chronic gingivitis) may persist indefinitely.

- Disease susceptible - inflammatory events extend apically and laterally to involve deeper connective tissues and alveolar bone.
- Proliferation of junctional epithelium - becomes increasingly permeable and ulcerated-- accelerating the ingress of bacterial products, and inflammation worsens.
Large no. of PMNS migrate

Secreting excessive amount of destructive enzymes & inflammatory mediators

Breakdown of structural components

MMPs (collagenases)

MMPs are the primary targets for host modulation
Host modulatory therapy can be used to interrupt these positive feedback loops and ultimately reduce the excessive levels of cytokines, prostanoids, and enzymes resulting in tissue destruction.

Macrophages recruited to area.
Activated (by binding to LPS) to produce prostaglandins (e.g., prostaglandin E2), interleukins (e.g., IL-1α, IL-1β, IL-6), TNF-α and MMPs.

The cytokines (interleukins and TNFα) and prostanoids are additional targets for modulatory therapeutics.

Interleukins and TNF-α bind to fibroblasts, which are stimulated to produce additional quantities of PGE₂, interleukins, TNFα and MMPs in positive feedback cycles.

Concentration of these enzymes and inflammatory mediators becomes pathologically high in the periodontal tissues.

Host modulatory therapy can be used to interrupt these positive feedback loops and ultimately reduce the excessive levels of cytokines, prostanoids, and enzymes resulting in tissue destruction.
MMPs breakdown collagen fibres, disrupting the normal anatomy of the gingival tissues - resulting in destruction of the pdl.

Inflammation extends apically, & osteoclasts are stimulated to resorb alveolar bone by the high levels of prostaglandins, interleukins, and TNF α in the tissues.

The osteoclasts themselves are targets for host modulation.

Drugs can be administered to down regulate osteoclastic activity and ultimately to inhibit bone resorption by these cells.
The elevations in the proinflammatory or destructive mediators are counterbalanced by elevations in anti-inflammatory or protective mediators such as the cytokines IL-4 and IL-10, as well as other mediators such as IL-1ra (receptor antagonist) and tissue inhibitors of matrix metalloproteinases (TIMPs).

Under health, anti-inflammatory or protective mediators serve to control tissue destruction.

Adequate levels of these anti-inflammatory or protective mediators keep the host response to the bacterial challenge in check, the individual will be disease-resistant.

If the imbalance occurs, with excessive levels of the proinflammatory or destructive mediators present in the host tissues, tissue destruction will ensue in the susceptible host.
• Purpose of host modulation therapy - restore the balance of proinflammatory or destructive mediators and anti inflammatory or protective mediators to that seen in the healthy individuals.

• Pocket formation occurs as coronal junctional epithelium is broken down and restored at a more apical location.

• Plaque bacteria then migrate apically along the root surface deeper into the pocket, where the physical conditions favour the proliferation of gram – negative anaerobic species.

• Bacterial products continue to challenge the host, and the host continues its frustrated response against these products. Inflammation extends further and further apically, more bone is resorbed.

• The pocket deepens, and the associated attachment and bone loss result in clinical and radiographic signs of periodontitis. Intervention is required to prevent eventual tooth loss and other sequelae of the disease.
Combination of therapeutic approaches --- best chance for clinical improvements

- Reduction in the burden (by root surface instrumentation and hygiene therapy).
- Risk factor modulation (by smoking cessation and improved diabetes control).
- Host response modulation.
Risk factors

- Genetic
- Environmental (e.g., tobacco use),
- Acquired risk factors (e.g. systemic disease) imbalance between the proinflammatory and anti inflammatory mediators
- Affect onset, rate of progression, and severity of periodontal disease as well as response to therapy.
Modified to reduce a patient’s susceptibility

### Risk Factors for Periodontal Disease

- Heredity: family history, PST test
- Smoking: frequency, current history, past history
- Diabetes: duration, control
- Stress: reported by patient
- Medications: calcium channel blockers, dilantin, cyclosporin, drugs known to cause dry mouth
- Nutrition
- Poor oral hygiene: plaque and calculus
- Faulty dentistry: overhangs, subgingival margins
- Hormonal variations: pregnancy (increased estradiol and progesterone), menopause (decreased estrogen, osteoporosis)
- Immunocompromise: HIV, neutropenia
- Connective tissue diseases
- Previous history of periodontitis
HOST RESPONSE MODULATION

• Down regulate destructive aspects of the host response
• Host response modulators offer the potential for modulating or reducing this destruction by ameliorating excessive or pathologically elevated inflammatory processes to enhance opportunities for wound healing and periodontal stability.
Drugs

Non steroidal anti-inflammatory drugs,

- Biphosphonates,
- Tetracyclines

- Growth factors
- Enamel matrix proteins
- Bone morphogenetic proteins
SYSTEMICALLY ADMINISTERED AGENTS
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

MOA:-

Inhibition of cyclooxygenase enzymes that participate in arachidonic acid metabolism

Reduction of prostanoid production, specially
MEMBRANE PHOSPHOLIPIDS

ARACHIDONIC ACID
MCQs
The predominant cell type in gingival crevicular fluid is the:
  ◦ Mast cells
  ◦ Plasma cells
  ◦ Macrophages
  ◦ Polymorphonuclear leukocytes

Gingival crevicular fluid is measured using:
  ◦ Whatman’s filter paper
  ◦ Mylar’s strip
  ◦ Ph paper
  ◦ Litmus paper

The predominant immunoglobulin in sulcular fluid is:
  ◦ Ig A
  ◦ Ig G
  ◦ Ig M
  ◦ Ig E
Drugs which reaches maximum concentration in gingival crevicular fluid:
- Tetracycline
- Penicillin
- Erythromycin
- Sulphonamide

Which cell type migrates into gingival sulcus in large numbers in response to dental plaque:
- Mast cells
- Neutrophils
- Lymphocytes
- Plasma cells

Sulcular fluid does not perform one of the following function:
- Contains plasma proteins which may improve adhesion
- Possess antimicrobial properties
- Exerts antibody activity
- Provides nutrition to junctional epithelium via diffusion
The most potent bone resorbing interleukin is:

- IL-8
- IL-1b
- IL-5
- IL-3

Plaque is considered as an infection because:

- Antibiotics prevents its formation
- Its presence is evidence of bacterial growth
- It is communicable between experimental animals and probably humans
- All of the above

The gingival crevicular fluid is increased in all except:

- Periodontal pocket
- Gingivitis
- Smoking
- Trauma from occlusion
Gingival fluid is:
- Transudate
- Exudates
- Can be either of two (a & b)
- Neither of two (a & b)