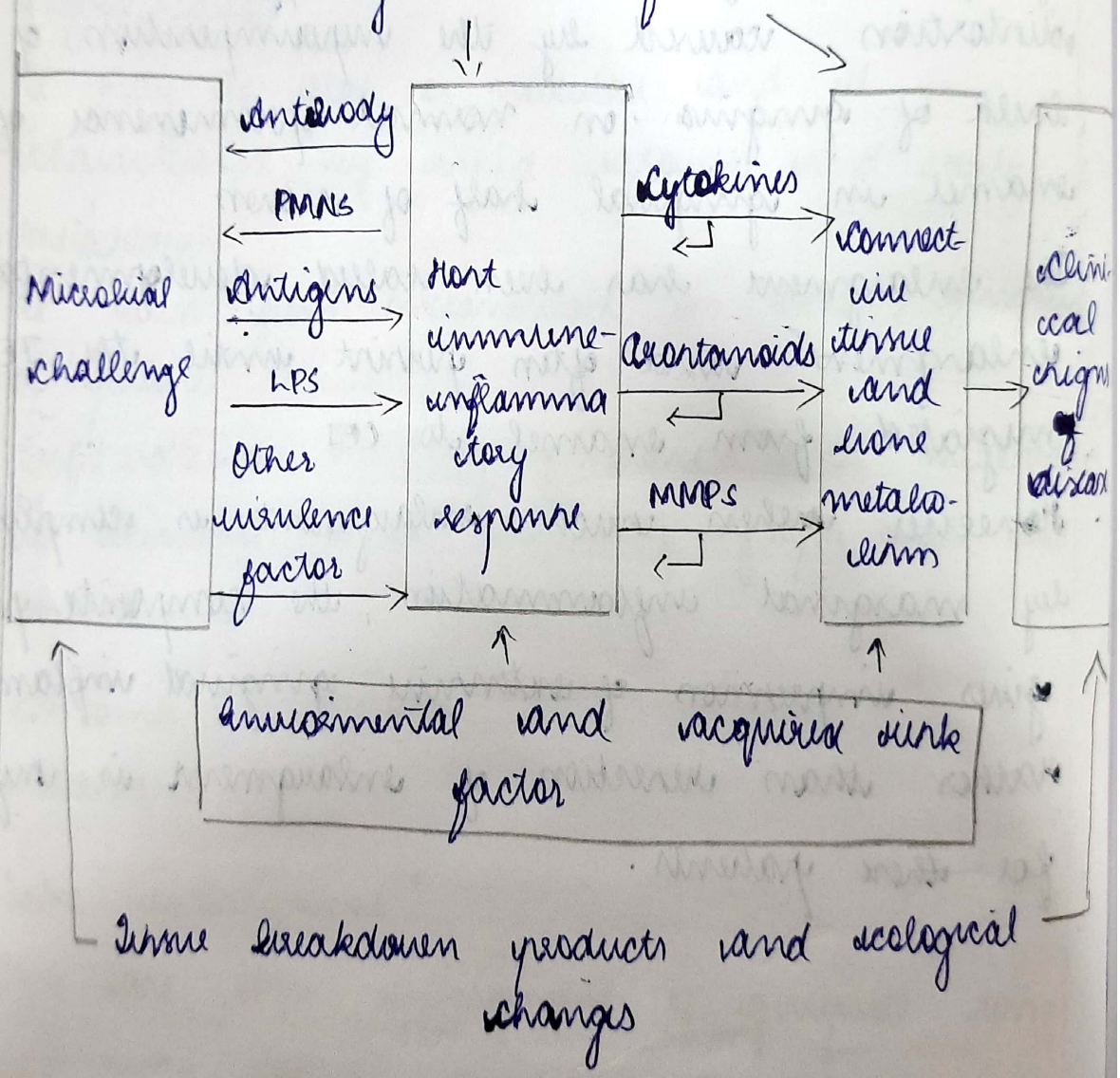
HOST MODULATION

It refers to the modulation of the immune response to suppress unwanted reaction to protect an organism against injurious disease is defined as host modulation

Pathogenesis of periodontitis by Page and Kornman



New Model of pathogenesis

Plaque

Overgrowth of Gram ve bacteria in susceptible individuals lead to gingival inflammation

Health → gingivitis → gingival inflammation later subgingival microenvironment

Host immune and inflammatory reaction together with genetic predisposition and environmental influence unable to 'contain' infection ← gingivitis

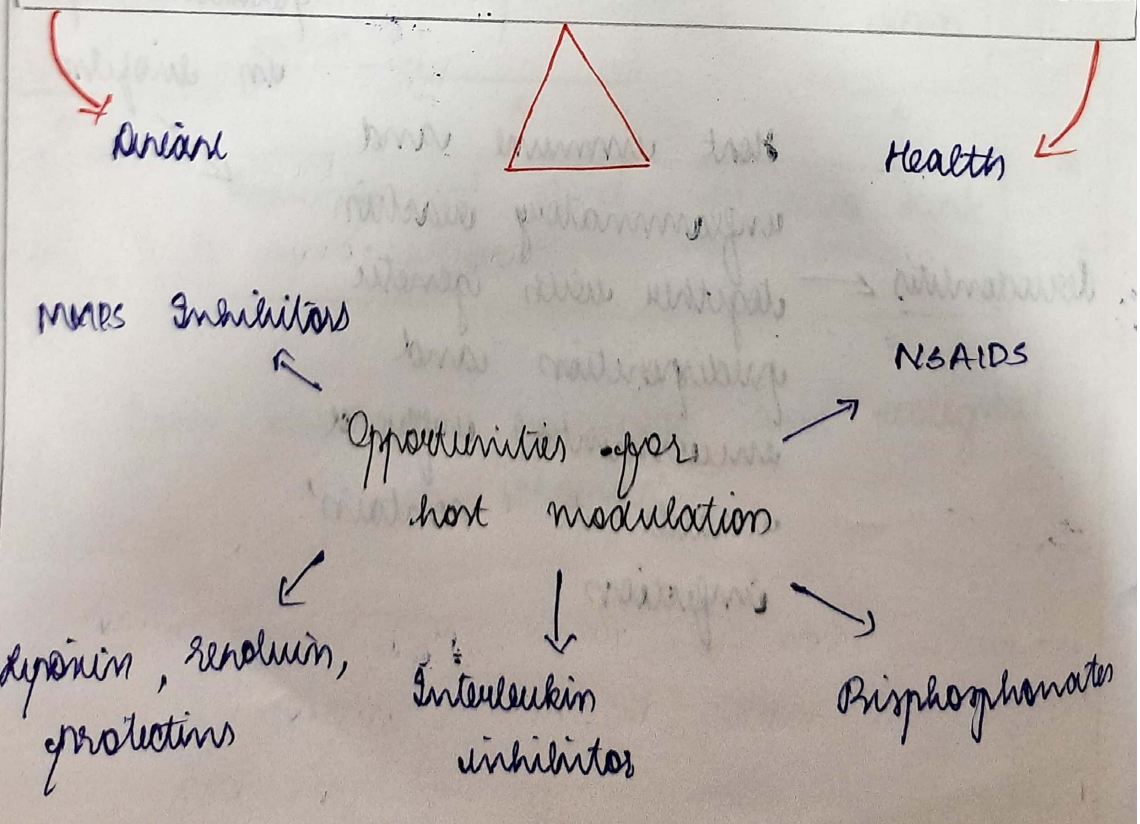
Overgrowth of 'periodontal pathogens' in biofilm

Host immune and inflammatory reaction together with genetic predisposition and environmental influence unable to 'contain' infection ← Periodontitis

Periodontal balance.

- Balance between periodontal disease and health

• Risk factors (eg - genetics smoking, diabetes)	• Reduction of risk factors
• Overproduction of pro-inflammatory or destructive mediators and enzyme. (eg; IL-1, IL-6, PGE_2, TNF-α, MMPs)	• Expression of host-derived anti-inflammatory or protective mediators (eg; IL-4, IL-10, IL-1α, TIMPs)
• Underactivity or overactivity of aspects of host response	• Host modulation therapy Resolution of inflammation
• Poor compliance, poor plaque control Subgingival microbes	• OHI, SRP, surgery, antiseptics antibiotics to reduce bacterial challenge



NSAIDS

- 2 isoforms of COX were recognized

↙

- COX-1 is expressed 'constitutively'
- Known as 'housekeeping' enzyme
- Functions include:-
  - gastric cytoprotection
  - Mesenteric homeostasis
  - Platelet aggregation
  - Kidney function

↘

- COX-2 is usually undetectable in most tissue
- Its expression is 'inducible' during states of inflammation
- Upregulated by pro inflammatory cytokines endotoxins

Classification

Non selective COX inhibitors

Salicylates – Aspirin
– Diflunisal

Pyrazalone derivatives – Phenylbutazone
– Oxyphenylbutazone

Indole derivatives – Indomethacin

Propionic acid derivatives – Ibuprofen
– Naproxen
– Ketoprofen

Antranilic acid derivatives – Mephenamic acid

Aryl acetic acid derivatives – Piroxicam
– Tenoxicam

Pyrrolo-pyrrol derivatives – Ketorolac

- analgesic - antipyretic with poor antiinflammatory action
Para-amino phenol derivatives - paracetamol
Pyrazole derivative - Metamizole
- Propyphenazole

- Preferential COX-2 inhibitors - Nimesulide
- Meloxicam
- Nabumetone

- Selective COX-2 inhibitors - Celecoxib
- Rofecoxib
- Valdecoxib

NSAIDs not used as an adjunctive in periodontal therapy
- GIT upset.
- Hepatic impairment
- Renal impairment
- Rebound effect
- Unwanted side effects of COX-2 inhibitors
GI hemorrhage.

Lysozyme, neurotoxins and protectins
Rationale
- Resolution of inflammation - biological pathway
on acute vasoactive mediated, return to tissue
homeostasis and biological pathway of restoring homeostasis

Lipoxins ← Therapeutic management → Resolvins

Therapeutic management → Protectins

Endogeneous mediators

- Lipoxins derived from arachnoidic acid
- Aspirin triggered lipoxin (ATL)
- Resolvins derived from omega 3 - PUFA
- Protectins derived from docosahexanoic acid

Resolvins derived from omega 3 - PUFA

- Eicosapentaenoic acid
  - Resolvin E series
- Docosahexanoic acid
  - Resolvin D series

Lipoxins

- Produced within macular lumen, primarily via platelet - leukocyte transcellular biosynthesis enzymatically generated from arachidonic acid, an omega - 6 fatty acid and are released during inflammatory response

Inhibit chemotaxis, adhesion and transmigration of neutrophils

Stimulate phagocytosis of apoptotic neutrophils by macrophages

Action of Lipoxin

In fibroblasts, lipoxins and ATL inhibit IL-1β stimulated production of IL-6 and IL-8

Inhibit chemotaxis, IL-5 and release generation by eosinophils

Resolvins

- Derived from the omega 3 PUFAs, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA).
- The co-administration of aspirin increases the stability and duration of action of resolvins and protectins

Matrix metallo proteinase

- mmps are zinc dependent and calcium requiring endopeptidase enzyme.
- Degrade extracellular matrix protein during organogenesis, growth and normal tissue turnover
- Transcription of mmp gene is up regulated by pro inflammatory cytokines
- mmps produced by both resident and inflammatory cell of periodontium play role in physiological

and pathological events

- fibroblast
- keratinocyte
- epithelial cell
- mast cell
- eosinophills
- PMNs

Action of MMPs inhibitors

Inhibit the synthesis or release of these enzyme

Block the activation of precursor form of MMPs

Stimulate the synthesis of endogenous tissue, inhibitors of MMPs

Protect the shed endogenous inhibitors from proteolytic inactivation

Exogenous (synthetic) inhibitors

- Zn and Ca chelating agents
- Phosphorous containing peptides
- Sulphur based inhibitors
- Hydroxamic acid inhibitors

endogeneous inhibitor

Pharmacological inhibitor

MMP
transcription
↓
Pro MMP

TIMP — ⊘ | ⊘ — synthetic MMP inhibitor
↓

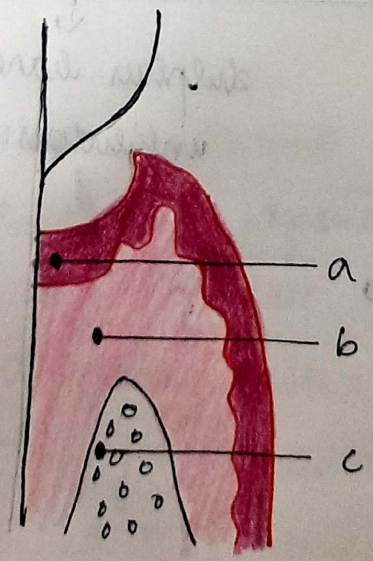
Active MMP

α_2 - macroglobulin → ↓

endocytosis and clearance by low density lipoprotein - receptor - related protein

Subantimicrobial - dose doxycycline

Mechanism of action



a- Inhibition of production of epithelial - derived MMPs by inhibiting cellular expression and synthesis

b- Direct inhibition of active MMPs by cation chelation

- Inhibition of oxidative activation of latent MMPs
- Downregulates expression of key inflammatory cytokines including IL-1, IL-6 and TNF-α
- Scavenges and inhibit production of reactive oxygen species produced by PMNs
- Inhibition of MMPs and ROS protects α, proteinase inhibitor, thusly indirectly reducing tissue proteinase activity
- Stimulate fibroblast collagen production

c- Reduce osteoclast activity and bone resorption

- Blocks osteoclast MMPs
- Stimulate osteoblast activity and bone formation

Bisphosphanates

- Bone sparing agent
- Bisphosphonates are analogs of pyrophosphate in which the oxygen is replaced by carbon with various side chain
- It bind to the hydroxyapatite crystals of bone and prevents their dissolution by interfering with osteoclast function.
- Used extensively in the managment of osteoporosis and other bone resorptive conditions

Classification

First generation (alkyl side chain)	Second generation (amino terminal group)	Third generation (cyclic side chain)
· Etidronate	· Alendronate · Pamidronate	· Risedronate

Anti cytokine therapy

- Infliximab
  - Allergic reactions
  - Difficulty in breathing
  - Low BP
- Etanercept
  - Infection
  - Hypersensitivity
- Anakinra
  - Infection
  - Immunogenicity
  - Malignancies

Other Agents

Statins

Osteoprotegerin

No inhibitors