HOST MODULATION THERAPY

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MDS

Host can be defined as " the organism from which the parasite obtain its nourishment" or in transplantation of tissue, "the individual who receive graft."

Modulation is defined as "alteration of function or status of something in response to a stimulus or an altered chemical or physical environment."

Concept of host modulation was **first introduced** by **Williams (1990) and Golub et al (1992)**

- Periodontist previously believed that periodontal disease was an consequence of aging and uniformly distributed

- Thought that severity was directly correlated with plaque

- Disease progression occurred in a continuous, linear manner throughout life.

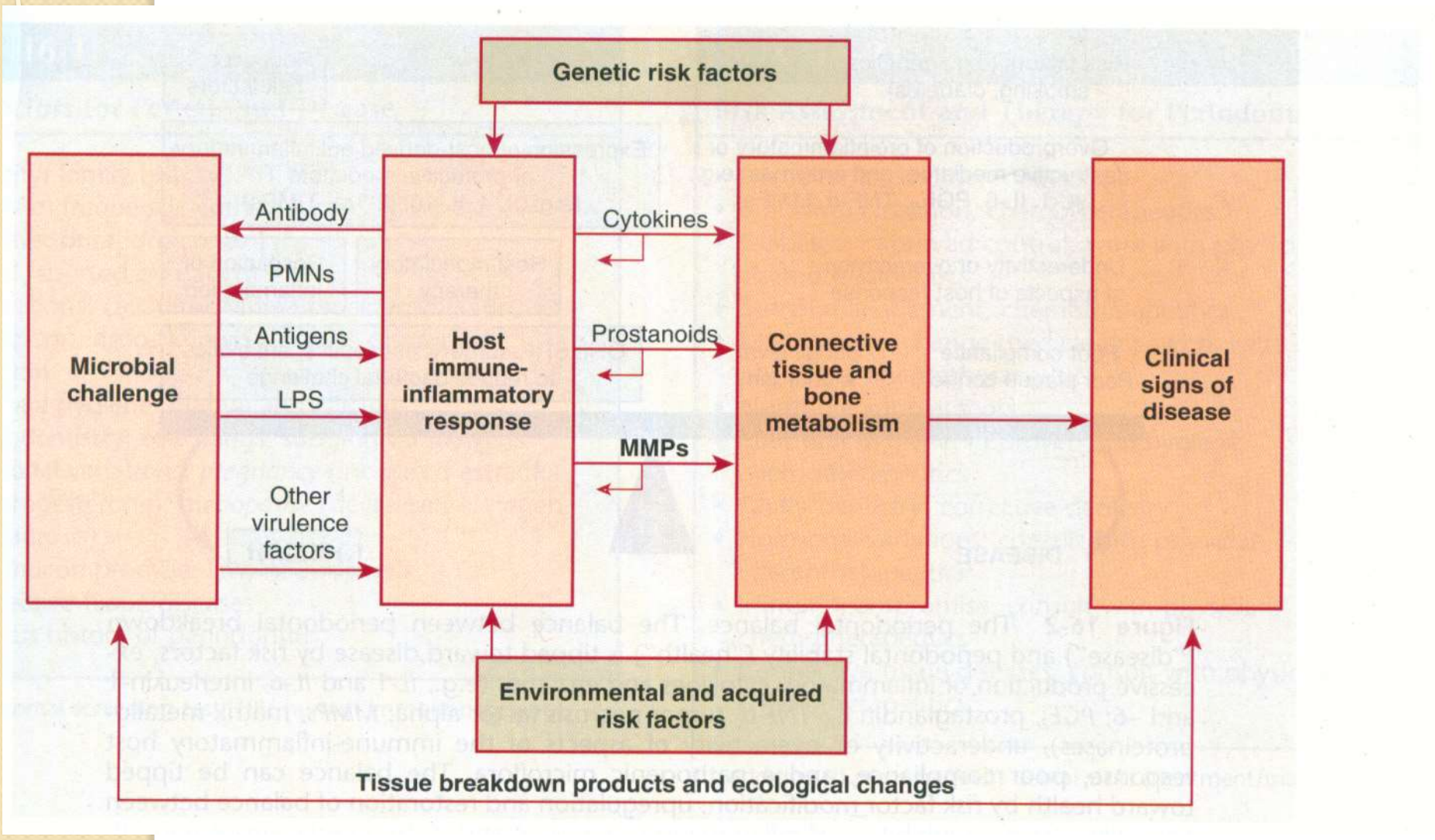
- Better epidemiological data, there has been shift about prevalence and progression of periodontitis.
- Well established that periodontitis is not related to ageing
- Disease severity is not correlated with plaque

- *Patients with abundant plaque and calculus deposits with widespread gingivitis but have minimum deep pocket*
- *In contrast: despite maintaining high standard of plaque control, succumb to aggressive form of periodontitis with deep pocket, tooth mobility and early tooth loss*
- *The former group of patients are periodontal disease resistant.*
- *Whereas the latter is periodontal disease susceptible.*

- Majority of the destructive events occurring in the periodontal tissues result from activation of destructive processes to plaque bacteria.

- Host response is essentially protective but paradoxically can also result in tissue damage: breakdown of connective tissue fibers in the periodontal ligament and resorption of alveolar bone.

- The nature of host response to the presence of plaque is modified by genetic factors(aggressive periodontitis) and systemic and environmental factors (smoking , diabetes , stress).


Genetic risk factors
Microbial challenge
Antibody
PMNs
Antigens
LPS
Other virulence factors
Host immune-inflammatory response
Cytokines
Prostanoids
MMPs
Connective tissue and bone metabolism
Clinical signs of disease
Environmental and acquired risk factors
Tissue breakdown products and ecological changes

- *To modify or reduce destructive aspect of host response: so that immune-inflammatory response to plaque is less damaging: host modulation therapy has been developed*

DEFINITION

- *HMT is a treatment concept that aims to reduce tissue destruction and stabilized or even regenerate the periodontium by modifying or down regulating destructive aspects of host response and up regulating protective or regenerative responses (Carranza).*

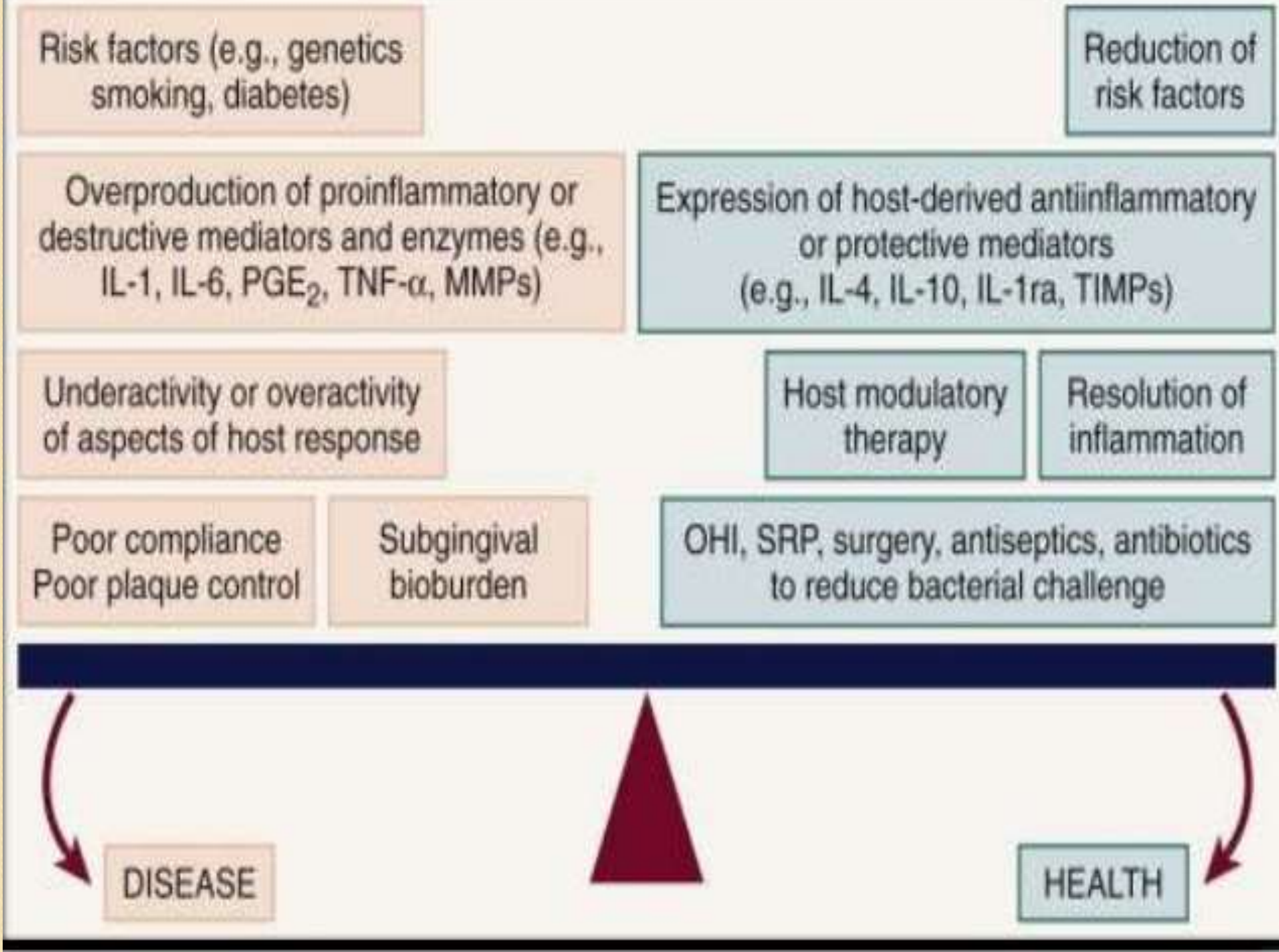
- HMTs are systemically or locally delivered pharmaceuticals that are prescribed as part of periodontal therapy and are used as adjuncts to conventional periodontal treatment.

- Historically, treatment has focused on reducing the bacterial challenge by the use of SRP, improved oral hygiene, and periodontal surgery.

- *However, the outcomes are not always predictable*

- **Periodontal disease and health can be seen as balance between**
  - Persisting bacterial burden and proinflammatory destructive events in the tissue.
  - Resolution of inflammation and downregulation of destructive process.

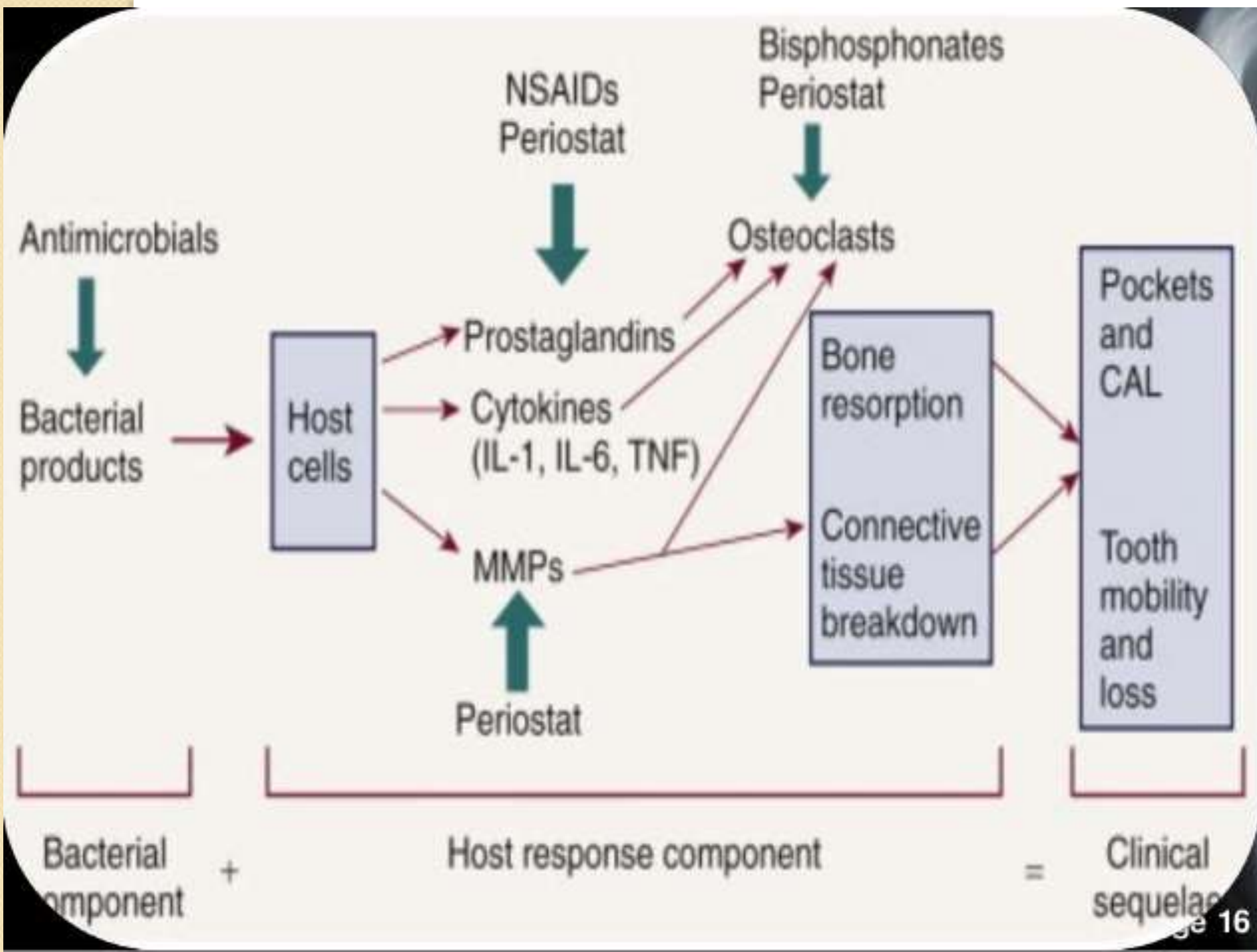
- *Bacterial challenge is never completely eliminated after SRP and recolonization occurs*.
  - HMTs offers the potential for downreguating destructive aspects and upregulating protective aspects of the host response.
- In Combination with conventional treatments to reduce the bacterial burden, the balance between health (resolution of inflammation and wound healing) and disease progression(continued proinflammatory events) is tipped in the direction of healing.


Risk factors (e.g., genetics smoking, diabetes)
Reduction of risk factors
Overproduction of proinflammatory or destructive mediators and enzymes (e.g., IL-1, IL-6, PGE_2, TNF-α, MMPs)
Expression of host-derived antiinflammatory or protective mediators (e.g., IL-4, IL-10, IL-1ra, TIMPs)
Underactivity or overactivity of aspects of host response
Host modulatory therapy
Resolution of inflammation
Poor compliance Poor plaque control
Subgingival bioburden
OHI, SRP, surgery, antiseptics, antibiotics to reduce bacterial challenge
DISEASE
HEALTH

- HMTs do not "switch off" normal defense mechanism or inflammation; instead , they ameliorate excessive of pathologically elevated inflammatory process to enhance opportunities for wound healing.

- **Specific aspects of disease pathogenesis for modulation**

a. *Regulation of immune and inflammatory responses.*
b. *Regulation of excessive production of MMPs*
c. *Regulation of arachidonic acid metabolites*
d. *Regulation of bone metabolism*


Bisphosphonates
Periostat
NSAIDs
Periostat
Antimicrobials
Osteoclasts
Pockets
and
CAL
Bacterial
products
Host
cells
Prostaglandins
Cytokines
(IL-1, IL-6, TNF)
Bone
resorption
Connective
tissue
breakdown
Tooth
mobility
and
loss
MMPs
Periostat
Bacterial
component
+
Host response component
=
Clinical
sequelae

HOST MODULATING AGENTS

- **Systemically administered agents**
  - ✓ NSAIDs
  - ✓ Bisphosphonates
  - ✓ Sub antimicrobial Dose Doxycycline
- **Locally administerd agents**
  - ✓ Topical NSAIDs
  - ✓ Enamel matrix proteins
  - ✓ Growth factors
  - ✓ Bone morphogenic proteins

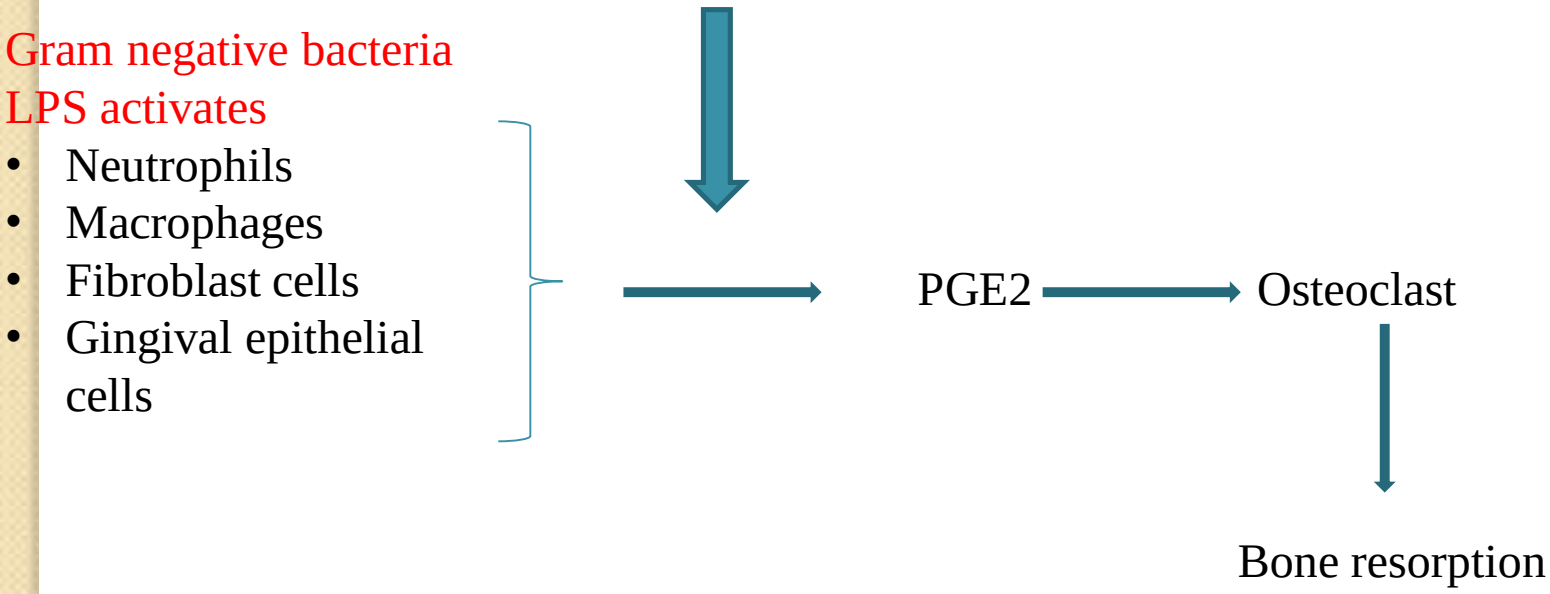
Non-steroidal Anti-inflammatory Drugs

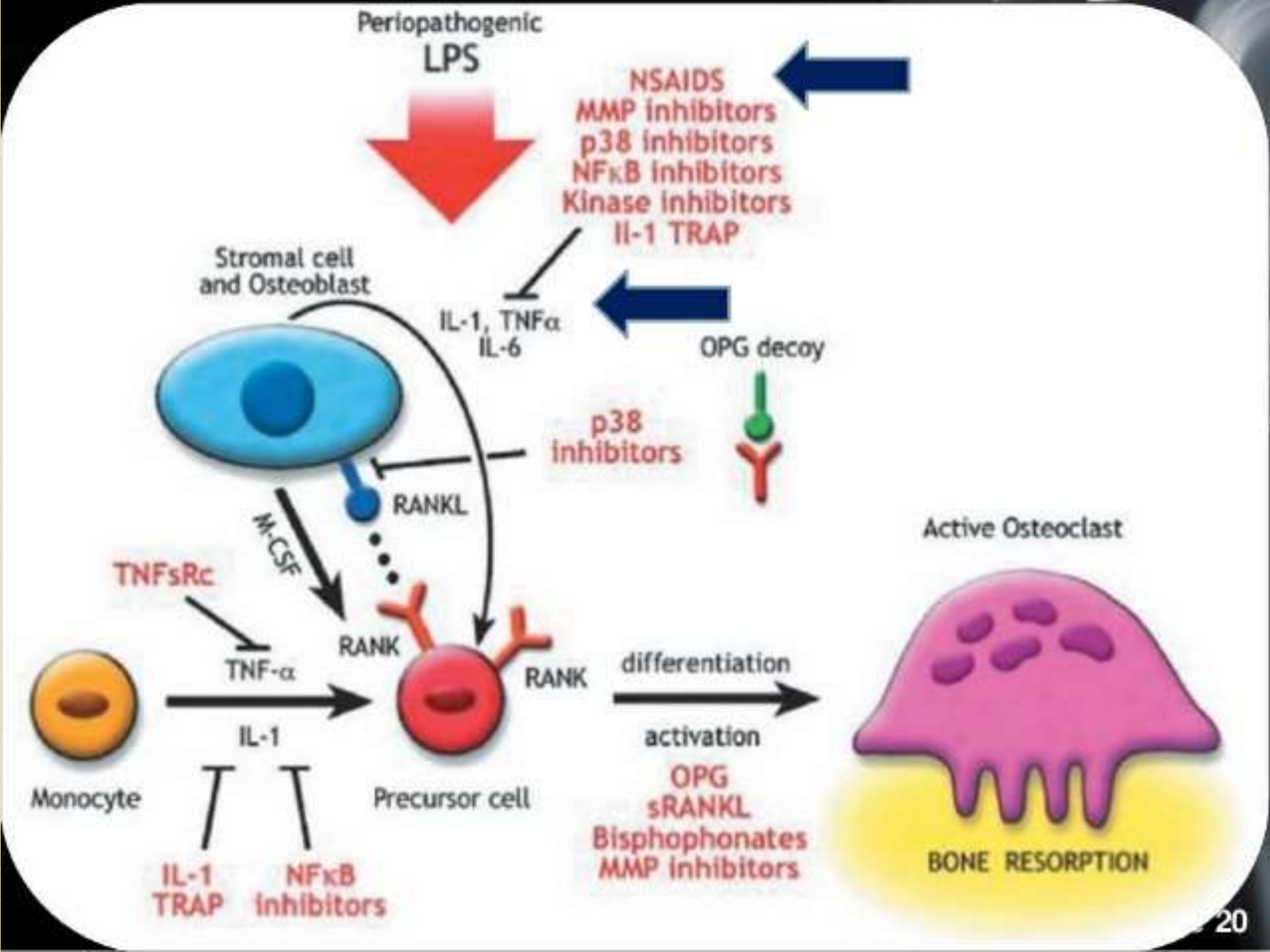
- NSAIDs inhibit the formation of prostaglandin, including prostaglandin E2 (PGE2) (Grenier et at 2002).
  - Produced by neutrophils, macrophages, fibroblasts, and gingival epithelial cells in response to lipopolysacharides (LPS).

- PGE2 Upregulates bone resorption by osteoclasts (Heasman PA and Colins P 1993)
- Levels of PGE2 elevated in patients with periodontitis (Plamondon and Sorsa jp 2002)
- It also inhibits fibroblast function and has inhibitory effects on the immune response (Grossi and Genco Ann periodontics 1997)

Mechanism

NSAIDS




Periopathogenic
LPS
NSAIDS
MMP inhibitors
p38 inhibitors
NFκB inhibitors
Kinase inhibitors
Il-1 TRAP
Stromal cell
and Osteoblast
IL-1, TNFα
IL-6
OPG decoy
p38
inhibitors
RANKL
M-CSF
TNFsRc
RANK
TNF-α
RANK
differentiation
IL-1
activation
Monocyte
Precursor cell
OPG
sRANKL
Bisphophonates
MMP inhibitors
IL-1
TRAP
NFκB
inhibitors
Active Osteoclast
BONE RESORPTION

Action

- Inhibits prostaglandins
- Reduce inflammation
  - Used to treat pain, acute inflammation and chronic inflammation
  - Inhibits osteoclastic activity in periodontitis (Howell TH 1993)
- NSAIDs such as indomithacin (Williams RC 1987), flurbiprofen (Jeffcoat MK1989) and Naproxen (Howell TH1993) administered up to 3 years, significantly slowed the rate of alveolar bone loss compared with placebo.

Disadvantages when used as a HMT for periodontitis

- Administration for extended periods is necessary for periodontal benefits to become apparent, and associated with significant side effects:
  - GIT problem,
  - Hemorrhage (from decrease platelet aggregation)
  - Renal and hepatic impairment.
- Research shows that the periodontal benefits of taking long term NSAIDs are lost when patients stop taking the drugs, with a return to or even an acceleration of the rate of bone loss seen before NSAID therapy , often referred to as a "rebound effect" (William RC 1991)

- use of selective COX-2 inhibitors reduce periodontal inflammation without the side effects typically observed after long-term (nonselective) NSAID therapy.

- selective COX-2 inhibitors slowed alveolar bone loss in animal models (Bezerra MM 1993) and modified prostaglandin production in human periodontal tissues. (Vardar S JPeriodontol 2003). However, the selective COX-2 inhibitors were later identified to be associated with significant and ***life-threatening adverse effects***, resulting in some drugs being withdrawn from the market.

SUMMARY,

NSAIDs (including the selective COX-2 specific inhibitors) are ***presently not indicated as adjunctive HMTs*** in the treatment of periodontal disease

Bisphosphonates

- The bisphosphonates are **bone-seeking agents** . inhibit bone resorption by disrupting osteoclast activity.

- **Interfere with osteoclastic metabolism** and secretion of lysosomal enzymes (Weinreb M et al J Periodontal 1994) possess **anticollagenase properties** (Nakaya H et al J Periodontol 2000)
- Treatment with the bisphosphonate significantly **increased bone density** compared with placebo (Reddy MS et al J Periodontol 1995)
- In human studies, these agents resulted in **enhanced alveolar bone status and density** (Rocha M et al J Periodontol 2001)
- The ability of bisphosphonates to modulate osteoclast activity clearly may be useful in the treatment of periodontitis,

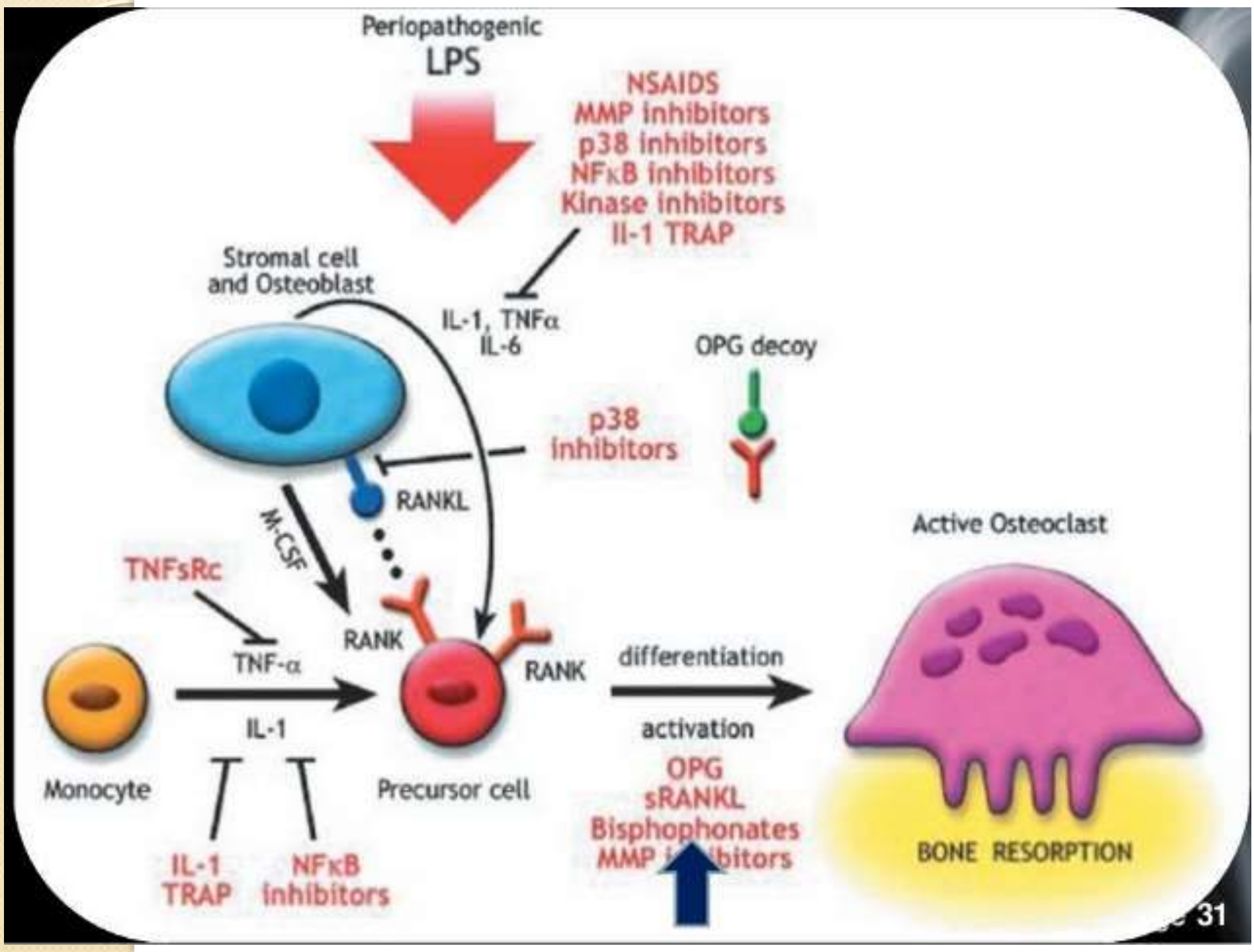
Some bisphosphonates have the unwanted effects

- inhibiting bone calcification
- inducing changes in white blood cell counts.
- avascular necrosis of the jaws following bisphosphonate therapy, with the resultant risk of bone necrosis following dental extractions (Carter G, Goss AN *Med J Aust* 2005)

- Bisphosphonate-related osteonecrosis of the jaw, although primarily associated with intravenous administration of bisphosphonates rather than oral administration,

- Has impeded the development of bisphosphonates as an HMT to manage periodontitis.

- As with NSAIDs, at present there are no bisphosphonate drugs that are approved and indicated for treatment of periodontal diseases


Periopathogenic
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differentiation
Active Osteoclast
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sRANKL
Bisphophonates
MMP inhibitors
BONE RESORPTION
IL-1
TRAP
NFκB
inhibitors

Sub-Antimicrobial Dose Doxycycline

- Sub-antimicrobial-dose doxycycline (SDD) is a 20-mg dose of doxycycline (Periostat) that is approved and indicated as an adjunct to SRP in the treatment of chronic periodontitis.
- It is taken twice daily for 3 months, up to a maximum of 9 months of continuous dosing.
- Therapeutic effect by enzyme, cytokine, and osteoclast inhibition rather than by any antibiotic effect.

- Studies have found no detectable antimicrobial effect on the oral flora or the bacterial flora in other regions of the body.

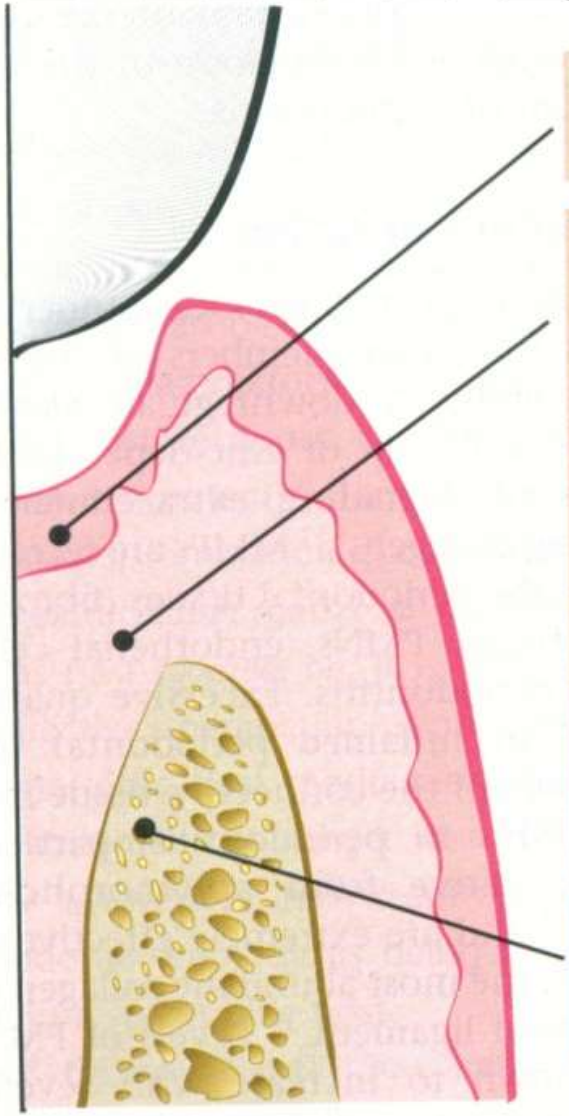
- At present SDD (Periostat) is the only systemically administered HMT specifically indicated for the treatment of chronic periodontitis that is approved by the US Food and Drug Administration (FDA) and accepted by the American Dental Association (ADA).

- Studies conducted by Preshaw et al in J Periodontol 2008 utilizing this same modified-release SDD versus placebo with periodontitis as an adjunct to SRP resulted in significantly greater clinical benefits than SRP alone in the treatment of periodontitis.

Mechanisms of Action

- Tetracycline's work well as host modulation agents because of their pleiotropic effects on multiple components of the host response .The only enzyme (MMP) inhibitors that have been approved for clinical use and tested for the treatment of periodontitis .

- Golub et al (J Periodont Res 1985). reported that the semisynthetic compound (e.g., doxycycline) was more effective than the parent compound tetracycline in reducing excessive collagenase activity in the GCF of chronic periodontitis patients.



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

- Direct inhibition of active MMPs by cation chelation (dependent on Ca^{2+} and Zn^{2+} binding properties)
- Inhibition of oxidative activation of latent MMPs (independent of cation-binding properties)
- Downregulates expression of key inflammatory cytokines including IL-1, IL-6, and TNF-α as well as PGE_2
- Scavenges and inhibits production of reactive oxygen species (ROS) produced by PMNs (e.g.HOCl, which activates latent MMPs)
- Inhibition of MMPs and ROS protects α_1 proteinase inhibitor (α_1-PI), thereby indirectly reducing tissue proteinase activity
- Stimulates fibroblast collagen production

- Reduces osteoclast activity and bone resorption
- Blocks osteoclast MMPs
- Stimulates osteoblast activity and bone formation

Figure 53-2 Schematic of periodontal pocket indicating the pleiotropic mechanisms by which doxycycline inhibits connective tissue breakdown. Downregulation of destructive events occurring in the periodontal tissues by doxycycline results from modulation of a variety of different proinflammatory pathways. (From Golub LM, Lee HM, Ryan ME, et al:

- The predominant MMPs in periodontitis, particularly MMP-8 and MMP-9, derive from PMNs (Golub LM et al J Clin Periodontol 1995) and are extremely effective in degrading type I collagen, the most abundant collagen type in gingiva and periodontal ligament (Mariotti A Periodontol 2000)

- Levels of PMN-type MMPs have been shown to increase with severity of periodontal disease and decrease after therapy (Golub LM, Ciancio et al J Periodontal Res 1990)

- The rationale for using SDD as a HMT in the treatment of periodontitis is that doxycycline downregulates the activity of MMPs by a variety of synergistic mechanisms, including reductions in cytokine levels, and stimulates osteoblastic activity and new bone formation by upregulating collagen production

- After cessation of SDD administration, however, there was a rapid rebound of collagenase activity , suggesting that a 1-month treatment regimen with this host modulation agent was insufficient to produce a long-term benefit(Ashley RA 1999)

- In contrast, during the same study, a 3-month regimen produced a prolonged drug effect without a rebound in collagenase levels to baseline during the no-treatment phase of the study.

Contraindications:

- History of **allergy or hypersensitivity** to tetracyclines.
- **Pregnant or lactating women** or children less than 12 years old (because of the potential for discoloration of the developing dentition).
- Reduce the efficacy of **oral contraceptive**.
- There is a risk of increased **sensitivity to sunlight** (manifested by an exaggerated sunburn) seen with higher doses of doxycycline, although this has not been reported in using the sub-antimicrobial dose.

Combining with Periodontal Surgery or Local Delivery Systems:-

- SDD can also be combined with the local delivery of antibiotics into the periodontal pocket through sustained-delivery systems. The two treatment approaches target different aspects of the pathogenic process:

–local delivery systems deliver antimicrobial concentrations of an antibacterial agent directly into the site of the pocket, whereas SDD is a systemic host response modulator.

- *(SRP + local antibiotics) can be combined with HMT (SDD) to maximize the clinical benefit for patients (Novak MJ J Periodontol 2008)*

Locally Administered Agents

- **Nonsteroidal Antiinflammatory Drugs**

- Topical NSAIDs have shown benefit in the treatment of periodontitis.
- Chronic periodontitis who received topical ketorolac mouth rinse reported that gingival crevicular fluid (GCF) levels of PGE2 were reduced by approximately half over 6 months and that bone loss was halted (Jeffcoat MK et al: J Periodontol 1995)
- Topically administered NSAIDs have not been approved as local HMTs for the management of periodontitis.

Enamel Matrix Proteins, Growth Factors, and Bone Morphogenetic Proteins:-

- Local HMTs used as adjuncts to surgical procedures, not only to improve wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus.
- **These have included**
  - *Enamel matrix proteins*
  - *Bone morphogenetic proteins (BMP-2, BMP-7),*
  - *Growth factors (platelet-derived growth factor)*
  - *Insulin like growth factor.*
  - *Tetracycline.*

- The locally applied HMTs currently approved by the FDA for adjunctive use during surgery are:

- Enamel matrix proteins (Emdogain),
- Recombinant human platelet-derived growth factor-BB (GEM 21S),
- BMP-2 (INFUSE).

EMERGING HOST MODULATORY THERAPIES

- In the future a variety of HMTs will likely be developed as adjunctive treatments for periodontitis. One of the most promising groups of potential HMTs is the *chemically modified tetracyclines* (CMTs).

- These nonantibiotic tetracycline analogs are tetracycline molecules that have been modified to remove all antibiotic properties, but which retain host modulatory, anticollagenolytic effects.

- The CMTs are also designed to be more potent inhibitors of proinflammatory mediators and can increase levels of antiinflammatory mediators such as interleukin-10 (IL-10).

- This would enable the clinician to increase the dose for patients with more risk factors and who might be more difficult to manage.

- CMTs such as CMT-3 and CMT-8 (both of which lack antibiotic activity but retain anti-MMP activity) have been shown to inhibit osteoclastic bone resorption and promote bone formation, enhance wound healing, and inhibit proteinases produced by periodontal pathogens (Greiner D et al 2002).

- CMTs also are being studied for other effects, such as inhibition of tumor cell invasion and attenuation of intimal thickening after arterial injury.

- CMTs will likely emerge as drugs that have beneficial effects in a variety of disease states because of their host modulation capabilities.

Summary

- Concept of periodontal medicine is emerging, in which dentist treats not only the bacterial challenge (eg. By SRP) but also the host side of the host bacterial interaction.

- The use of HMTs such as SDD offers the opportunity to improve the treatment outcomes.

- HMTs are an emerging treatment concept in the management of periodontitis


Thank You