Pathogenesis of periodontal diseases

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Pathogenesis

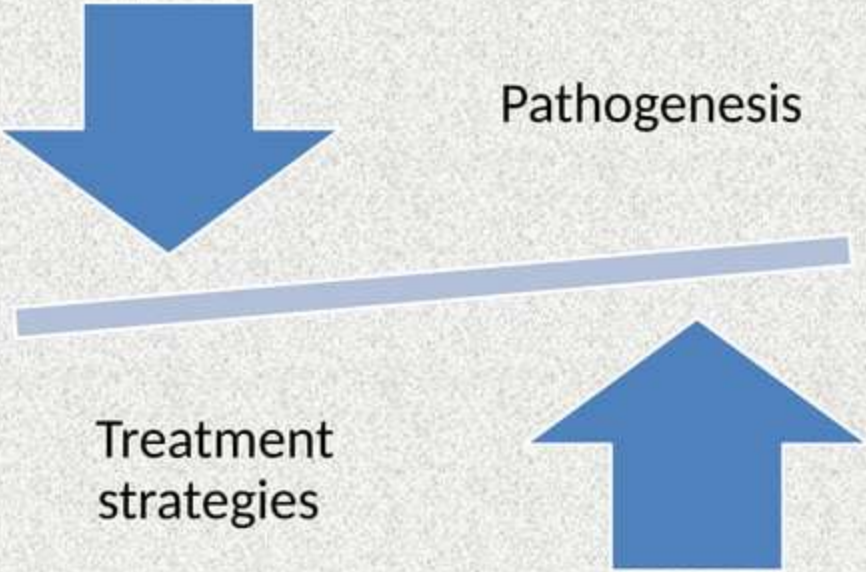
The word pathogenesis is defined as “the origination and development of a disease.”

The word itself is derived from the Greek roots pathos (meaning “suffering”) and genesis (meaning “generation or creation”)

step-by-step processes that lead to the development of a disease and that result in a series of changes in the structure and function.

Why is studying periodontal pathogenesis important?

- Understanding the disease processes is important because it may lead to the development of improved treatment strategies.


Pathogenesis
Treatment strategies

Course of periodontal diseases

Gingivitis precedes periodontitis, but it is clear that not all cases of gingivitis progress to periodontitis. In gingivitis, the inflammatory lesion is confined to the gingiva;

however, with periodontitis, the inflammatory processes extend to additionally affect the periodontal ligament and the alveolar bone.

The net result of these inflammatory changes is the breakdown of the fibers of the periodontal ligament, resulting in clinical loss of attachment together with resorption of the alveolar bone

Nature of periodontal diseases

- Complex inflammatory diseases
- Multifactorial
- Not an infection in the classic sense of the word.
- Periodontal disease, many species are identifiable in the periodontal pocket, and it is impossible to conclude that a single species or even a group of species causes periodontal disease.
- Bacterial and host response

Periodontal Pathogenesis Based on Description of Histopathological Features

Initial Lesion (Corresponds With Clinically Healthy Gingival Tissues)

- Slightly elevated vascular permeability and vasodilation
- Gingival crevicular fluid flows out of the sulcus
- Migration of leukocytes, primarily neutrophils, in relatively small numbers through the gingival connective tissue, across the junctional epithelium, and into the sulcus

Early Lesion (Corresponds With Early Gingivitis That Is Evident Clinically)

- Increased vascular permeability, vasodilation, and gingival crevicular fluid flow
- Large numbers of infiltrating leukocytes (mainly neutrophils and lymphocytes)
- Degeneration of fibroblasts
- Collagen destruction that results in collagen-depleted areas of the connective tissue
- Proliferation of the junctional and sulcular epithelium into collagen-depleted areas

Established Lesion (Corresponds With Established Chronic Gingivitis)

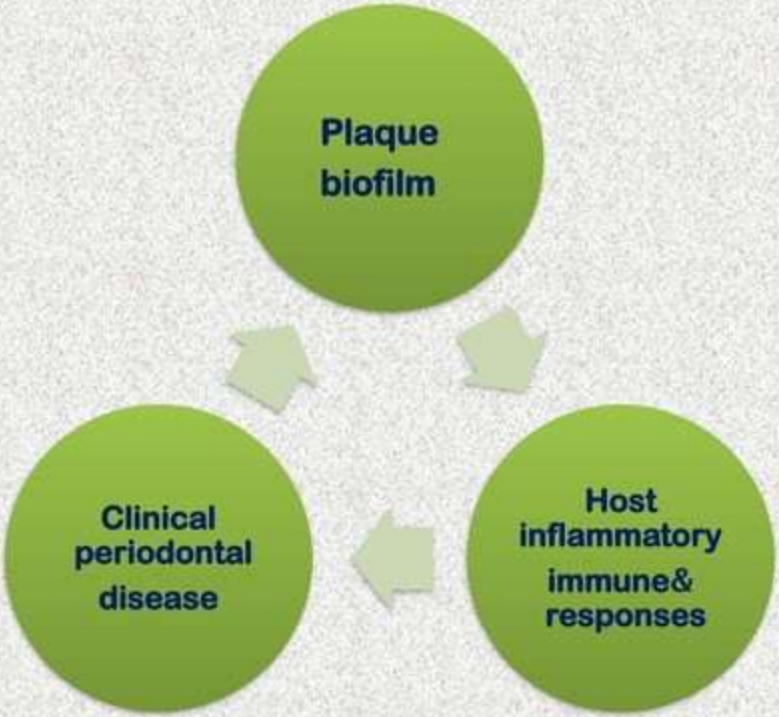
- Dense inflammatory cell infiltrate (i.e., plasma cells, lymphocytes, and neutrophils)
- Accumulation of inflammatory cells in the connective tissues
- Elevated release of matrix metalloproteinases and lysosomal contents from neutrophils
- Significant collagen depletion and proliferation of epithelium
- Formation of pocket epithelium that contains large numbers of neutrophils

Advanced Lesion (Marks the Transition From Gingivitis to Periodontitis)

- Predominance of neutrophils in the pocket epithelium and in the pocket
- Dense inflammatory cell infiltrate in the connective tissues (primarily plasma cells)
- Apical migration of junctional epithelium to preserve an intact epithelial barrier
- Continued collagen breakdown that results in large areas of collagen-depleted connective tissue
- Osteoclastic resorption of alveolar bone

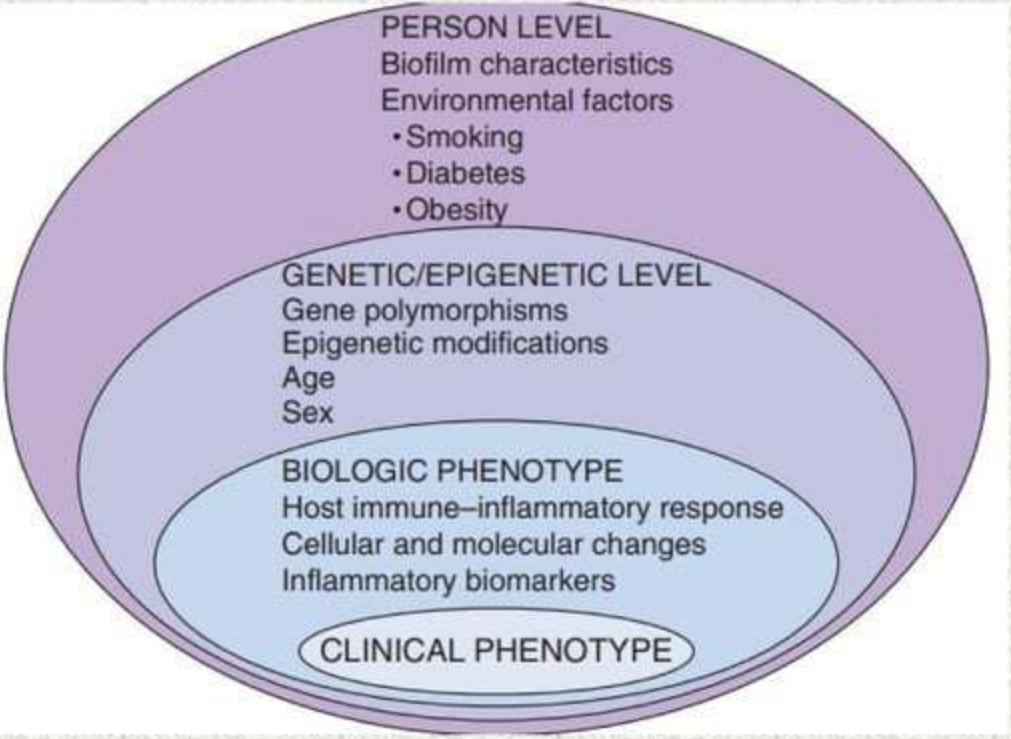
Current Paradigm of Periodontal Pathogenesis

According to the most well-established pathogenesis paradigm, ***periodontal disease is the result of a*** *complex interplay between microbial challenge, host response, and other modifying factors.*


Plaque biofilm
Host inflammatory immune& responses
Clinical periodontal disease

The inflammatory & immune processess that develop in the periodontal tissues in response to the long-term presence of the subgingival biofilm ***are protective by intent*** but result in tissue damage known as **bystander damage.**

A biologic systems model of periodontitis



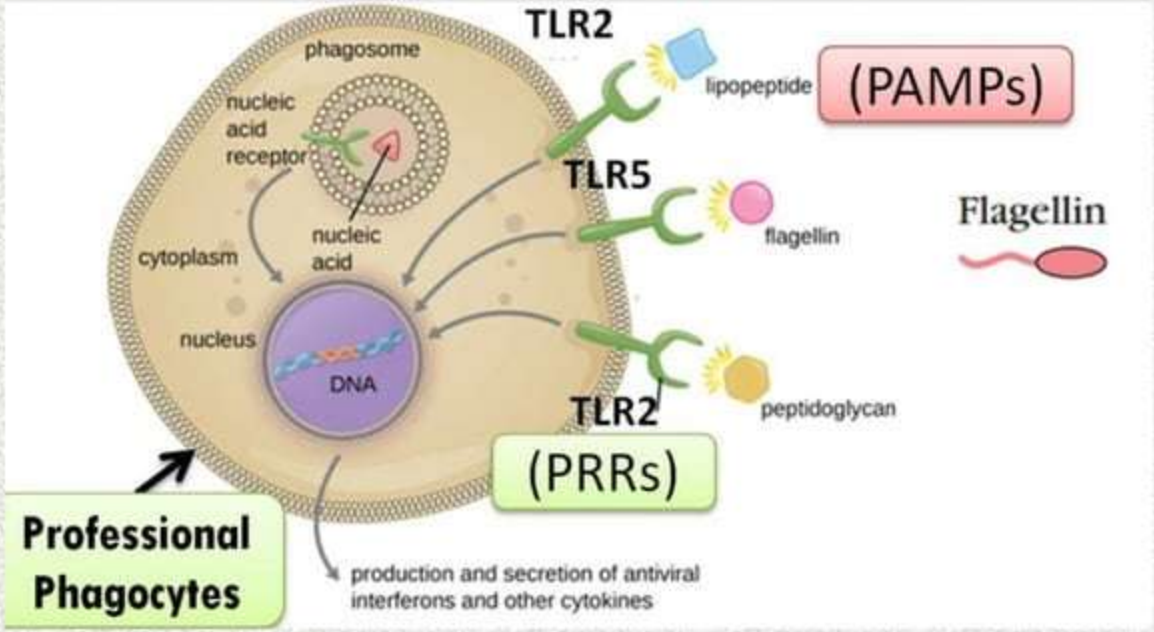
Microbial interaction with host response

Pathogen Recognition

Direct recognition of MAMPs (microbe associated molecular patterns)and PRRs(pattern recognition receptors).

Different types of PRRs as:

I. TLR(Toll-like receptors).
II. Nod (Nucleotide-oligomerization domain)protein like-receptor.
III. G-protein –coupled receptors.

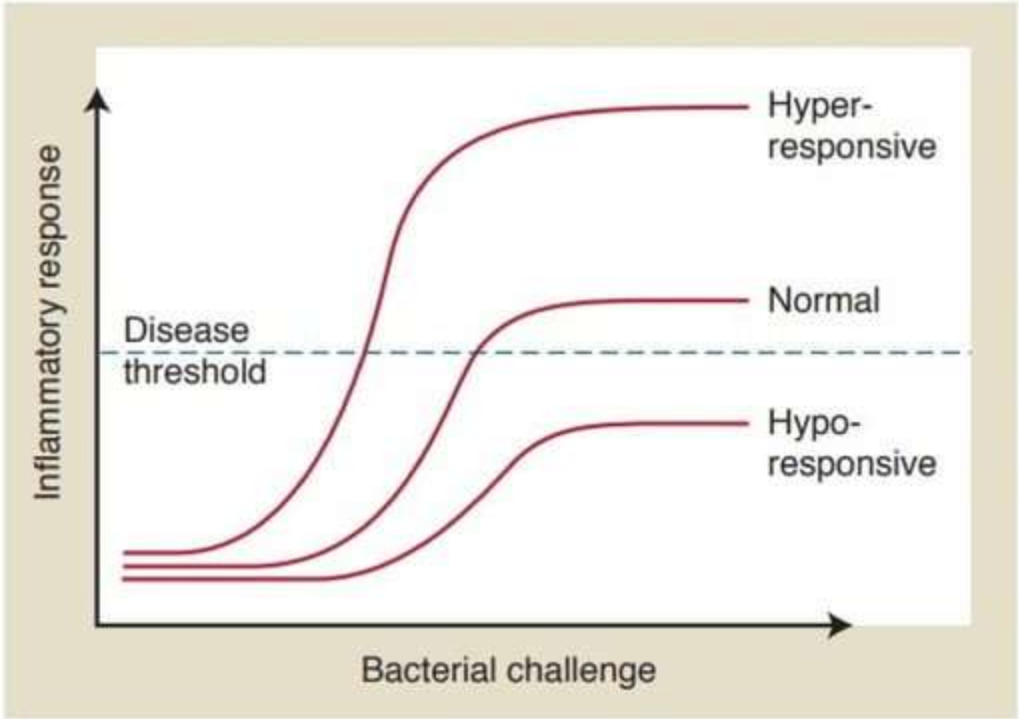

TLR2
phagosome
nucleic acid receptor
lipopeptide
(PAMPs)
TLR5
nucleic acid
cytoplasm
flagellin
Flagellin
nucleus
DNA
TLR2
peptidoglycan
(PRRs)
Professional Phagocytes
production and secretion of antiviral interferons and other cytokines

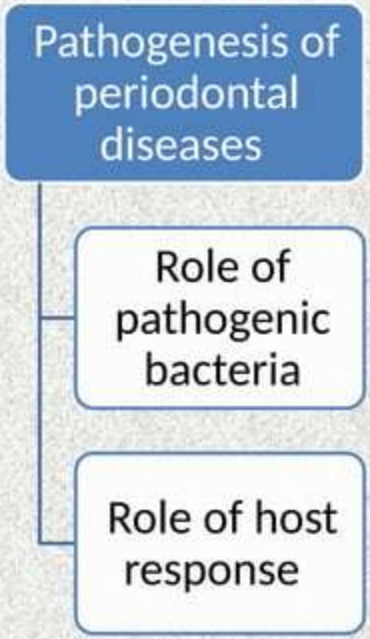
Inflammatory Responses in the Periodontium

The molecules that play a role in the pathogenesis of periodontitis	Microbial virulence factors
	Host immune–inflammatory response.

In terms of the relative importance of each, it is now clear that most of the tissue breakdown results from the host's inflammatory processes

Inflammatory response characteristics in relation to bacterial challenge




Pathogenesis of periodontal diseases
Role of pathogenic bacteria
Role of host response

Microbial Virulence Factors

Role of pathogenic bacteria

I. The subgingival biofilm ***initiates*** inflammatory responses in the gingival and periodontal tissues.
II. The subgingival bacteria also contribute ***directly to tissue damage*** by the release of noxious substances
III. Activating immune–inflammatory responses that, in turn, result in tissue damage

Microbial Virulence Factors

- Lipopolysaccharide
- Bacterial Enzymes and Noxious Products
- Microbial Invasion
- Fimbriae
- Bacterial Deoxyribonucleic Acid and Extracellular Deoxyribonucleic Acid

I. Lipopolysaccharide

- Lipopolysaccharides (LPSs) are large molecules composed of a lipid component (lipid A) and a polysaccharide component.
- Outer membrane of gram-negative bacteria,
- Act as endotoxins (LPS is frequently referred to as endotoxin)
- Elicit strong immune responses in animals
- Fundamental for maintaining structural integrity of the bacteria.

Lipopolysaccharide

- Interacts with the CD14/TLR-4/MD-2 receptor complex on immune cells such as macrophages, monocytes, dendritic cells, and B cells, with resulting release of proinflammatory mediators such as cytokines from these cells.

II. Bacterial Enzymes and Noxious Products

- Plaque bacteria produce several metabolic waste products that contribute directly to tissue damage.
- Noxious agents such as ammonia (NH_3) and hydrogen sulfide (H_2S),
- Short-chain carboxylic acids such as butyric acid and propionic acid.

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Short chain fatty acid

- These acids are detectable in GCF and are found in **increasing concentrations** as the severity of periodontal disease increases.
- The short-chain fatty acids may aid *P. gingivalis* infection through tissue destruction, and they may also create a nutrient supply for the organism by increasing bleeding into the periodontal pocket.
- The short-chain fatty acids also influence ***cytokine secretion*** by immune cells, and they may potentiate inflammatory responses after exposure to proinflammatory stimuli such as LPS, interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α)

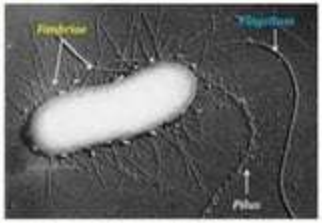
Proteases

- Plaque bacteria produce proteases, which are capable of breaking down structural proteins of the periodontium such as collagen, elastin, and fibronectin.
- Bacteria produce these proteases to digest proteins and thereby provide peptides for bacterial nutrition.
- Bacterial proteases disrupt host responses, compromise tissue integrity, and facilitate the microbial invasion of the tissues.

III. Microbial Invasion

- In histologic specimens, bacteria (including cocci, filaments, and rods) have been identified in the intercellular spaces of the epithelium.
- Periodontal pathogens such as P. gingivalis and Aggregatibacter actinomycetemcomitans have been reported to invade the gingival tissues, including the connective tissues.
- Fusobacterium nucleatum can invade oral epithelial cells, and bacteria that routinely invade host cells may facilitate the entry of noninvasive bacteria by coaggregating with them It has also been shown that A. actinomycetemcomitans can invade epithelial cells and persist

IV. Fimbriae



- The fimbriae of certain bacterial species, particularly P. gingivalis, may also play a role in periodontal pathogenesis as the following:

➢ P. gingivalis fimbriae ***stimulate*** immune responses, such ***as IL-6 secretion***, and the major fimbrial structural component of P. gingivalis, FimA, has been shown to stimulate ***nuclear factor (NF)-κB*** and ***IL-8*** in a gingival epithelial cell line through TLR

➢ ***Monocytes are also stimulated*** by P. gingivalis FimA, ***secreting IL-6, IL-8, and TNF-α***.

➢ ***inhibit IL-12 production***

- P. gingivalis **fimbriae also interact with complement receptor-3 (CR-3)** to activate intracellular signaling **pathways that inhibit IL-12 production** mediated by TLR-2 signaling. ***This may be of clinical relevance*** because IL-12 is important in the activation of natural killer (NK) cells and CD8+ cytotoxic T cells, which themselves may be important in killing P. gingivalis–infected host cells, such as epithelial cells.
- Indeed, the blockade of the CR-3 receptor promotes IL-12–mediated clearance of P. gingivalis and negates its virulence.

Bacterial fimbriae are therefore important for modifying and stimulating immune responses in the periodontium.

Host-Derived Inflammatory Mediators

The inflammatory and immune processes that develop in the periodontal tissues in response to the long-term presence of the subgingival biofilm are protective by intent but can result in considerable tissue damage, thereby leading to the clinical signs and symptoms of periodontal disease.

I. Cytokines

- Cytokines play a fundamental role in inflammation, and they are key inflammatory mediators in periodontal disease.
- They are soluble proteins, and they act as messengers to transmit signals from one cell to another.
- Cytokines bind to specific receptors on target cells and initiate intracellular signaling cascades that result in phenotypic changes in the cell by altered gene regulation.

I. Cytokines

- Proteins that transmit signals from one cell to another
- Bind to cell surface receptors to trigger production of protein by the cell
- There are proinflammatory and antiinflammatory cytokines.

Proinfalmmatory cytokines:

IL-1β, TNF α, IL-6, IL-8, Prostanoids.

- Cytokines and adaptive immune responses:

  Th1, Th2, Th17, Treg cytokines.
- Cytokines that mediate bone resorption.
- Mediators of C.T. destruction.

A key proinflammatory cytokine is ***interleukin-1β,*** which up-regulates inflammatory responses and is produced by multiple cell types in the periodontium

Antiinflammatory mediators & cytokines

- Lipoxins & Resolvins : inhibit neutrophil respones.
- IL-1RA: IL-1 receptor antagonist.
- Soluble TNFR: soluble TNF α receptor.
- Antiinflammatory cytokines:

  IL-10, IL-13 TGFβ (transforming growth factorβ).

Cytokine	Systematic Name	Function
IL-1α	IL-1F1	Intracellular protein, proinflammatory, contributes to bone resorption, functions as an intracellular transcriptional regulator
IL-1β	IL-1F2	Key role in inflammation and innate immunity, synergizes with other proinflammatory mediators, major role in adaptive immunity (i.e., regulation of T cells and myeloid cells), stimulates connective tissue breakdown and bone resorption
IL-1Ra	IL-1F3	Inhibits the action of IL-1α and IL-1β
IL-18	IL-1F4	Similar proinflammatory profile to IL-1β, activates neutrophils, synergizes with IL-12 to activate T-helper 1 cells
IL-1F5	IL-1F5	Antiinflammatory effects via IL-4 induction, antagonizes IL-1F6 action
IL-1F6	IL-1F6	Proinflammatory but restricted expression (e.g., localized to skin)
IL-1F7	IL-1F7	Antiinflammatory, acts as an intracellular regulator, reduces production of lipopolysaccharide-stimulated proinflammatory cytokines
IL-1F8	IL-1F8	Proinflammatory but restricted expression (e.g., localized to skin and synovial tissues)
IL-1F9	IL-1F9	Proinflammatory but restricted expression (e.g., localized to skin, placenta, and esophagus)
IL-1F10	IL-1F10	Putative antagonist with antiinflammatory action
IL-33	IL-1F11	Activation of T-helper 2 cells and mast cells, functions as an intracellular transcriptional regulator but restrict expression (e.g., endothelial cells, smooth muscle cells, and fibroblasts)

- In periodontal diseases, cytokines have wide range of overlapping actions as they are exposed to chronic bacterial challenge with persisitant chronic inflammation.
- *The balance between pro and anti-inflammatory cytokines determines the extent of periodontal tissue destruction*

II. Prostaglandins

- Lipid compounds derived from arachidonic acid
- Prostaglandin E2 (PGE2) is a key inflammatory mediator, stimulating production of other inflammatory mediators and cytokine production.
- PGE2 also stimulates bone resorption and plays a key role in periodontitis progression
- PGE2 results in the induction of MMPs and osteoclastic bone resorption, and it has a major role in contributing to the tissue damage that characterizes periodontitis.

III. Matrix Metalloproteinases

- A group of enzymes that break down structural proteins of the body MMPs include collagenases, which break down collagen.
- Key MMPs in periodontitis include MMP-8 and MMP-9, which are produced by neutrophils as they migrate through the periodontal tissues, thus contributing to periodontal tissue breakdown.

MMP Type	Enzyme	Biologic Activity
Collagenases	All	Degrade interstitial collagens (types I, II, and III) Digest ECM and non-ECM molecules
	MMP-1	Keratinocyte migration and re-epithelialization Platelet aggregation
	MMP-13	Osteoclast activation
Gelatinases	All	Degrade denatured collagens and gelatin
	MMP-2	Differentiation of mesenchymal cells with inflammatory phenotype Epithelial cell migration Increased bioavailability of MMP-9
Stromelysins	All MMP-3	Digest ECM molecules Activate pro-MMPs Disrupted cell aggregation Increased cell invasion

MMPs

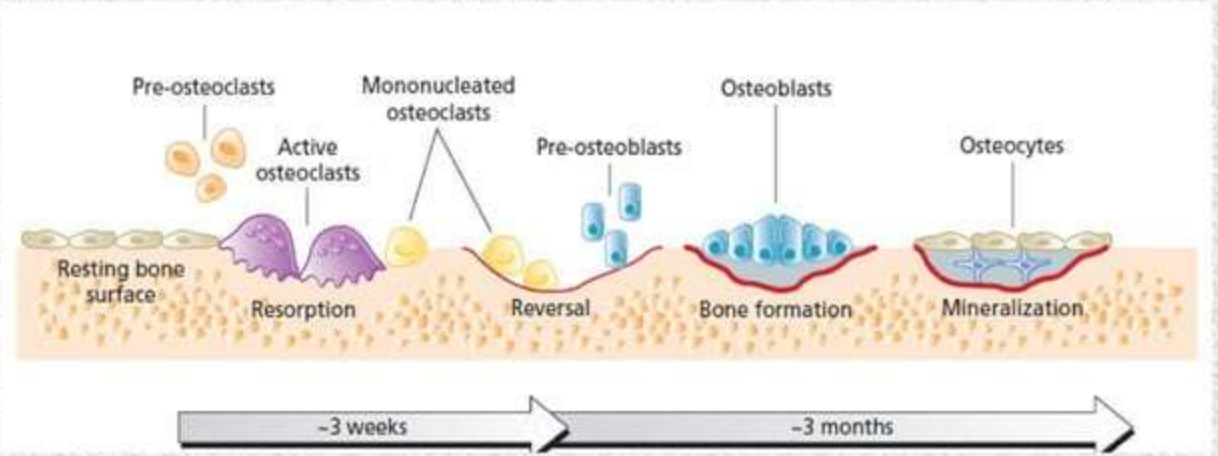
Matrilysins	MMP-7	Disrupted cell aggregation Increased cell invasion
Membrane-type MMPs	All	Digest ECM molecules Activate pro-MMP-2 (except MT4-MMP)
	MT1-MMP	Epithelial cell migration Degrade collagen types I, II, and III

VI. Tumor Necrosis Factor Alpha

- TNF-α is a key inflammatory mediator in periodontal disease
- Shares many of the cellular actions of IL-1β.
- It plays a fundamental role in immune responses, it increases neutrophil activity, and it mediates cell and tissue turnover by inducing MMP secretion.
- TNF-α stimulates the development of osteoclasts and limits tissue repair by the induction of apoptosis in fibroblasts.
- TNF-α is secreted by activated macrophages, as well as by other cell types, particularly in response to bacterial LPS.
- The proinflammatory effects of TNF-α include the stimulation of endothelial cells to express selectins that facilitate leukocyte recruitment, the activation of macrophage IL-1β production, and the induction of PGE2 by macrophages and gingival fibroblasts.

Alveolar bone resorption

Bone remodeling



Bone remodeling

- It is the process of replacement of old bone by new bone.
- It is a continuous process throughout the adult life.
- It involves coordinated actions of both osteoblasts and osteoclasts.
- The bone turnover is a steady state; the bone lost is balanced by bone formation.

Alveolar bone resorption

The failure to encapsulate the inflammatory response in the gingival tissues leads to its expansion to the alveolar bone.

Two critical factors determine whether bone loss occurs:

1. The concentration of inflammatory mediators in the gingival tissues must be sufficient to activate the pathways that lead to bone resorption.
2. The inflammatory mediators must penetrate to within a critical distance of the alveolar bone.

Alveolar bone resorption

- Histologic studies have confirmed that the bone resorbs so that a width of non-infiltrated connective tissue of about 0.5 to 1.0 mm overlying the bone is always present.
- ***Bone resorption stops completely when there is at least 2.5mm between the site of bacteria in the pocket & the bone.***

Alveolar bone resorption

- Osteoclasts are stimulated by proinflammatory cytokines and other mediators of inflammation to resorb the bone
- Osteoclasts are multinucleated cells that are formed from osteoclast progenitor cells and macrophages, and osteoclastic bone resorption is activated by a variety of mediators (e.g., IL-1β, TNF-α, IL-6, PGE2)

Alveolar bone resorption

RANK/RANKL/OPG System

RANK (receptor activator of nuclear factor-κB)	Cell surface receptor on osteoclast progenitor cells
RANKL (RANK ligand)	Cytokine-like molecule that is the ligand for RANK (i.e., binds to RANK) and causes maturation into fully differentiated osteoclasts
OPG (osteoprotegerin)	Cytokine-like molecule that binds to RANKL and inhibits the interaction between RANKL and RANK

The RANK/RANKL/OPG signaling pathway plays a key role in regulating bone resorption. RANKL binds to RANK and stimulates osteoclast differentiation and activation. OPG antagonizes this action by binding to RANKL and preventing it from binding to RANK. The ratio of RANKL to OPG is important, with studies reporting higher levels of RANKL and lower levels of OPG in patients with advanced periodontitis compared with healthy controls.

Thanks