Etiology of Periodontal Diseases(2)

Host-Microbe Interactions

Periodontology I

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Outline

- Basic concepts of immunity & inflammation
  - Cells of the immune system
  - Complement system
  - Leukocyte functions
  - T-Lymphocytes, B-lymphocytes and antibodies

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Outline

- Inflammatory response in the periodontium
  - Microbial virulence factors
  - Host-derived inflammatory mediators
- Immune responses in periodontal pathogenesis
  - Innate immunity
  - Adaptive immunity

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Outline

- Alveolar bone resorption
- Concept of host susceptibility

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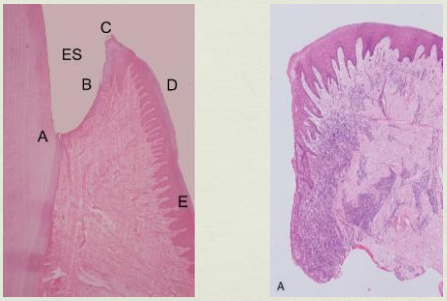
Periodontium: Health & Disease



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Periodontium: Health & Disease

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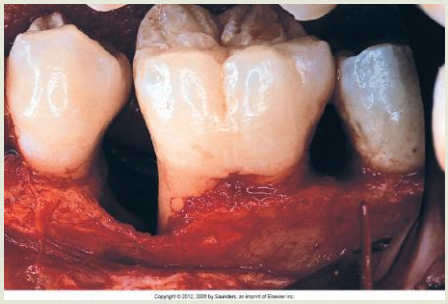

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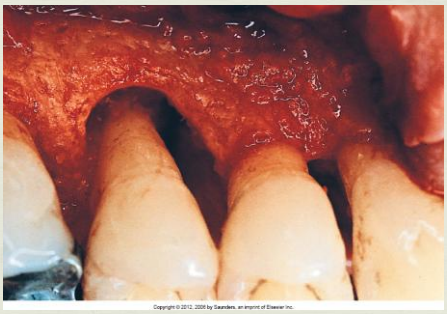

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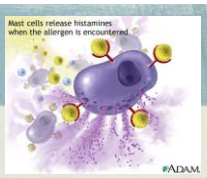
Immune cells



- Mast cells:
  - Immediate inflammation
  - Receptors for complement and IgG & IgE
  - Vasoactive substances: vasodilation and vascular permeability
  - Histamine, Heparin, ECF, NCF & others

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Immune cells

- Dendritic cells:
  - Leukocytes with cytoplasmic projections
  - professional APC's
  - expresses MHC II and other cell adhesion and costimulatory molecules

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Immune cells

- Neutrophils & Monocytes/Macrophages
  - 2/3 of leukocytes, phagocytic, APC's
  - PMN: phagocytic, lysosomes, receptors for complement and IgG
  - Monocyte/Macrophages: blood & tissue, chronicity, receptors for complement, Ig's, MHC II & others

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Immune cells

- Lymphocytes (T-cells):
  - Cytokines
  - CD4, CD8
  - recognizes antigen associated with MHC I or II on APC's
  - CD4: humoral response / CD8: cytotoxic

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Immune cells

- Lymphocytes (B-cells):
  - APC's
  - Plasma cells & memory cells
  - Antibodies
  - Cytokines

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Immune cells

- Lymphocytes (NK-cells):
  - recognize antigens with MHC I, MHC I or other surface GP
  - Auto-regulation

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Complement System

- 30 soluble or membrane-associated GP
- Classical, Lectin or Alternative pathways
- Functions:
  - Vasoactive
  - Anaphylaxis
  - Chemotaxis
  - Opsonization

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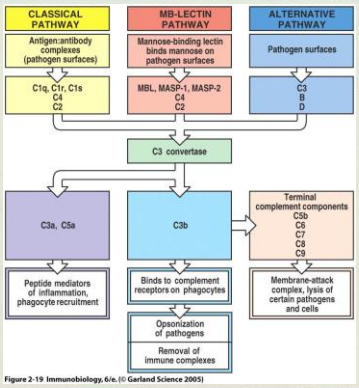

Figure 2-19 Immunobiology, 6/e. © Garland Science 2005)

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Leukocyte Functions

- Chemotaxis
- Phagocytosis
- Antigen processing and presentation

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Leukocyte Functions

- Chemotaxis
  - Movement of leukocytes along a chemotactic gradient (bacterial or host derived)
  - assumes a polarized shape

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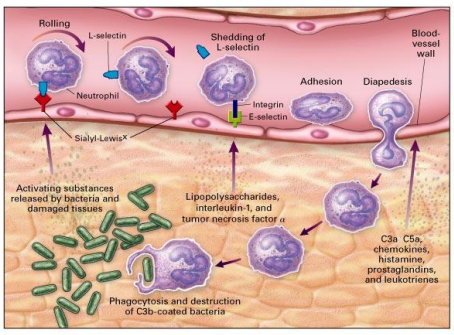

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Leukocyte Functions

- Phagocytosis
  - The process by which cells ingest particles of a size visible to light microscopy.
  - Killing mechanisms:
    - Oxidative killing
    - non-oxidative killing

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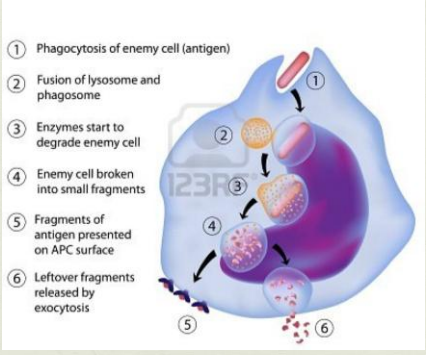

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Leukocyte Functions

- Antigen processing and presentation
  - MHC II -->CD4+ cells
  - co-stimulation
  - Toll-like recpetors

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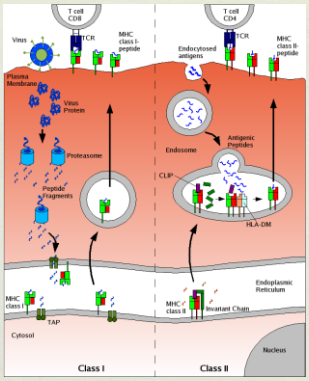

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T-Lymphocytes

- CD4 and CD8: cell surface molecules; functional T-cell subsets
- CD4+ is the predominant phenotype in a the stable periodontitis lesion
- B-cell-dominated destructive lesion

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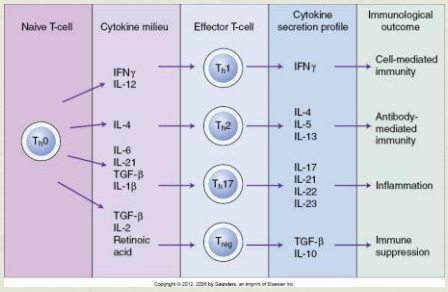

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B-Lymphocytes & Antibodies

- Plasma cells - antibody production
- Mostly IgG, some IgM and IgA
- Low biologic activity

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- Inflammatory response in the periodontium
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Microbial Virulence Factors

- Lipopolysaccharide (LPS):
  - Outer membrane of G-ve bacteria
  - Endotoxin
  - Highly conserved in bacterial species
  - recognized by TLR-4

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Microbial Virulence Factors

- Lipopolysaccharide (LPS):
  - *P. gingivalis* LPS is atypical in being recognized by TLR-2 and TLR-4
    - Lipotechoic acid - G+ve bacteria

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Microbial Virulence Factors

- Bacterial enzymes and noxious products:
  - Direct: direct damage to host cells
  - Indirect: potentiating the immune response

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Microbial Virulence Factors

- Bacterial enzymes and noxious products:
  - Ammonia NH_3
  - Hydrogen sulfide H_2S
  - Butyric & propionic acid

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Microbial Virulence Factors

- Bacterial enzymes and noxious products:
  - Proteases
  - Gingipains in *P.gingivalis*

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Microbial Virulence Factors

- Microbial invasion:
  - *Aa* and *Pg*
  - Invasion of epithelial and connective tissues
  - Intra-cellular invasion

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Microbial Virulence Factors

- Fimbriae: *Pg* FimA
- Bacterial DNA and exrta-cellular DNA

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Host Inflammatory Mediators

- Cytokines
- Prostaglandins
- Matrix Metalloproteinases

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Host Inflammatory Mediators

- Cytokines:
  - Soluble proteins that function as messengers and transmitting signals between cells
  - Binding to receptors initiates an intra-cellular signaling cascade resulting in altering gene regulation and ultimately affecting the cell phenotype and function

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Host Inflammatory Mediators

- Cytokines:
  - Produced by many cells
  - Primarily, acts locally
  - Positive feedback
  - Significant overlap and redundancy

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Host Inflammatory Mediators

- Cytokines:
  - IL-1β:
  - produced mainly by monocytes, macrophages and neutrophils
  - elevated in sites affected by periodontal disease

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Host Inflammatory Mediators

- Cytokines:
  - TNFα:
  - secreted by activated macrophages
  - MMP secretion, development of osteoclasts, apoptosis of fibroblasts, leukocyte recruitment, IL-1β & PGE_2 secretion

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Host Inflammatory Mediators

- Prostaglandins:
  - Lipid compounds derived from the degredation of arachidonic acid found in the cell membranes of most cells.

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Host Inflammatory Mediators

- Prostaglandins:
  - COX-1 & COX-2
  - COX-2 upregulated by IL-1β, TNFα, LPS
  - PGE_2 induces MMP's & osteoclasts

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Host Inflammatory Mediators

- Matrix Metalloproteinases:
  - A family of Zinc-dependent proteolytic enzymes that degrade extracellular matrix molecules such as collagen, gelatin, and elastin

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Host Inflammatory Mediators

- Matrix Metalloproteinases:
  - In the periodontium, secreted by most cells
  - Very important for maintenance and turnover of connective tissue

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Host Inflammatory Mediators

- Matrix Metalloproteinases:
  - Upregulated by IL-1β & TNFα
  - Contributes to the breakdown of connective tissue and bone

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TABLE 21-1 -- Classification of Matrix Metalloproteinases

Group	Enzyme	Name
Collagenases	MMP-1	Collagenase 1, fibroblast collagenase
	MMP-8	Collagenase 2, neutrophil collagenase
	MMP-13	Collagenase 3
Gelatinases	MMP-2	Gelatinase A
	MMP-9	Gelatinase B
Stromelysins	MMP-3	Stromelysin 1
	MMP-10	Stromelysin 2
	MMP-11	Stromelysin 3
Matrilysins	MMP-7	Matrilysin 1, pump-1
	MMP-26	Matrilysin 2
Membrane-type MMPs	MMP-14	MT1-MMP
	MMP-15	MT2-MMP
	MMP-16	MT3-MMP
	MMP-17	MT4-MMP
	MMP-24	MT5-MMP
	MMP-25	MT6-MMP
Others	MMP-12	Macrophage elastase
	MMP-19	—
	MMP-20	Enamelysin

Adapted from Hannas AR, Pereira JC, Granjeiro JM, et al: Acta Odontol Scand 65:1-13, 2007.

MMPs, Matrix metalloproteinases; *MT*, membrane type.

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Innate Immunity

- Saliva
- Epithelial tissues
- GCF
- Pathogen recognition
- Neutrophil function

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Innate Immunity

- Saliva:

TABLE 21-4 -- Constituents of Saliva that Contribute to Innate Immunity

Saliva Constituent	Host Defense Function
Antibodies (e.g., IgA)	Inhibit bacterial adherence, promote agglutination
Histatins	Neutralize LPS, inhibit destructive enzymes
Cystatins	Inhibit bacterial growth
Lactoferrin	Inhibits bacterial growth
Lysozyme	Lyses bacterial cell walls
Mucins	Inhibits bacterial adherence, promotes agglutination
Peroxidase	Neutralizes bacterial hydrogen peroxide

IgA, Immunoglobulin A; *LPS*, lipopolysaccharides.

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Adaptive Immunity

- T-cells
- B-cells
- Antibodies

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Outline

- Alveolar bone resorption
- Concept of host susceptibility

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Alveolar Bone Resorption

- Osteoclast:
  - cell responsible for bone resorption
  - derived from OPC/monocytes
  - resorption stimulated by wide range of mediators

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Alveolar Bone Resorption

- Critical factors:
  1. Concentration of mediators
  2. Distance from bone
- RANK/RANKL/OPG pathway

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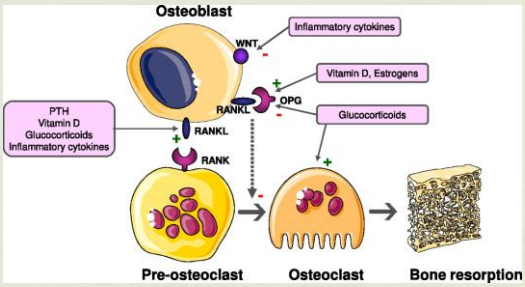

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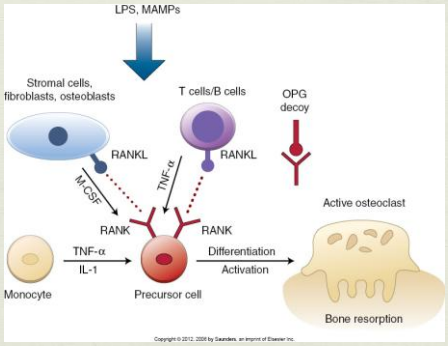

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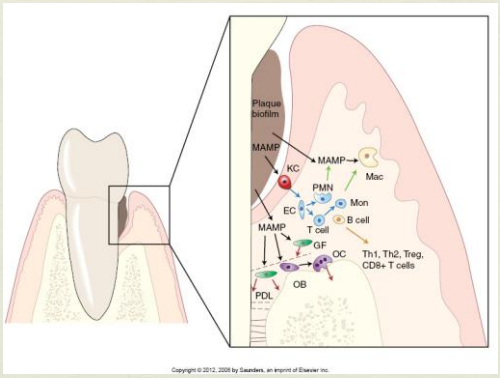

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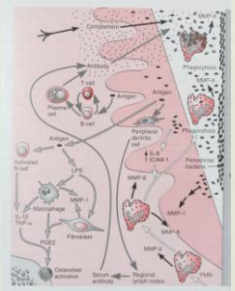
Putting everything together..



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Outline

- Alveolar bone resorption
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Host Susceptibility

- The subgingival biofilm --> complex immune/inflammatory response --> mediated by a large number of pro- & anti-inflammatory cytokines
- This occurs with a backdrop of other host and environmental factors

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Host Susceptibility

- "Hyper-inflammatory trait"
- Polymorphism
- Epigenetics

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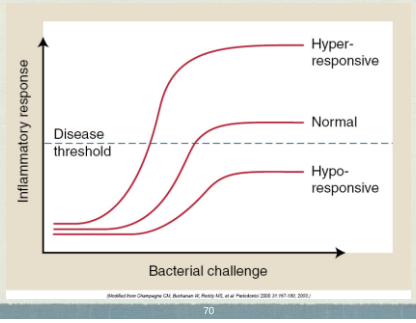
Host Susceptibility



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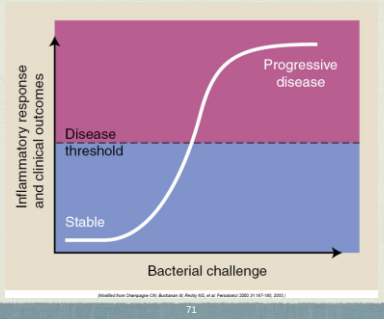
Host Susceptibility



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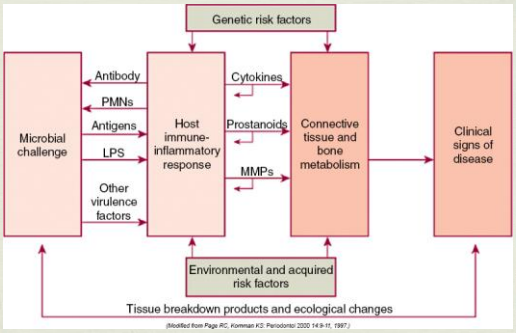

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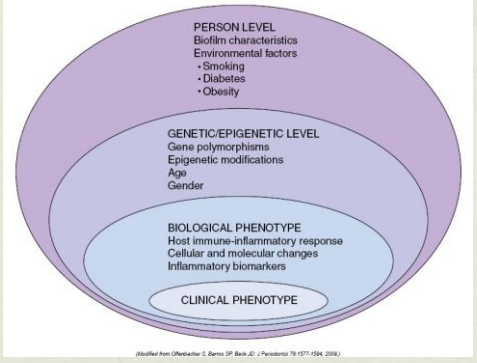

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References:

- Carranza's Clinical Periodontology 11th edition: chapter 21 "Periodontal Pathogenesis"

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