

Immunity, Inflammation and the Etiology of Periodontitis

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Objectives

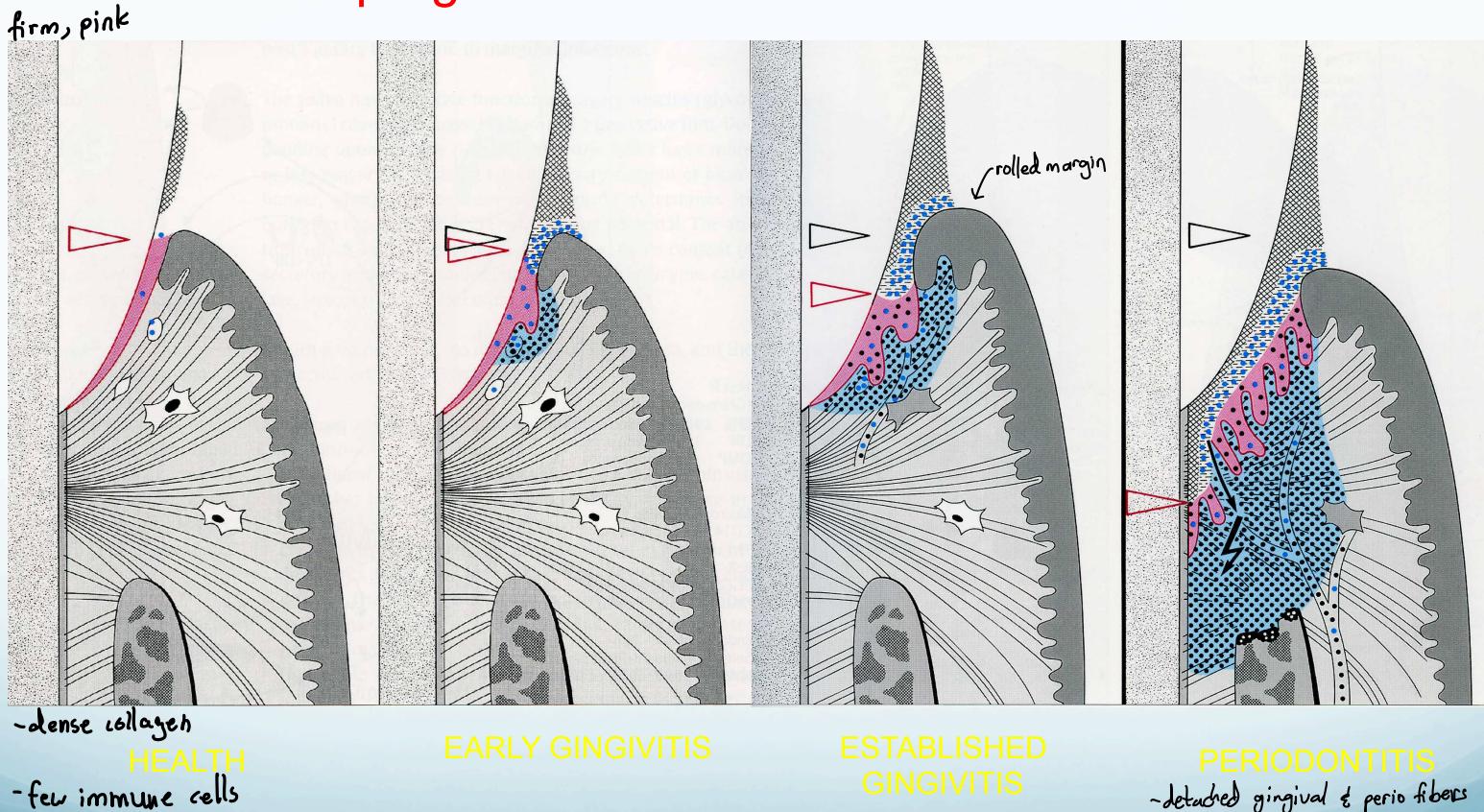
- You should be able to describe the protective and potentially destructive roles of the innate and adaptive host responses
- You should be able to describe the role of neutrophils, and macrophage in periodontitis
- You should be able to describe the roles of T cells and B cells in the host response in periodontitis
- You should be able to describe the mechanism of tissue destruction in the periodontitis lesion

How/Why does Periodontitis Occur?

- Direct destruction of tissues by periodontal pathogens by their virulence factors (e.g. proteases)?
- Failure of the host^{immune} response to protect the periodontal tissues from invading periodontitis associated bacteria?
- Immunopathology, “friendly fire”

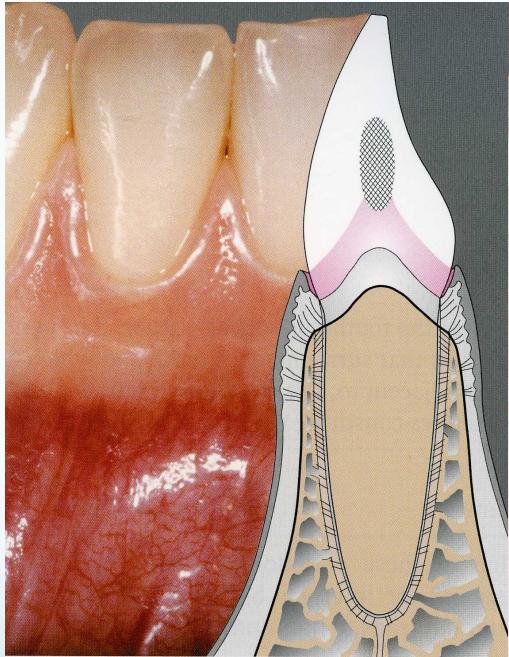
*rewatch

The progression from health to Periodontitis

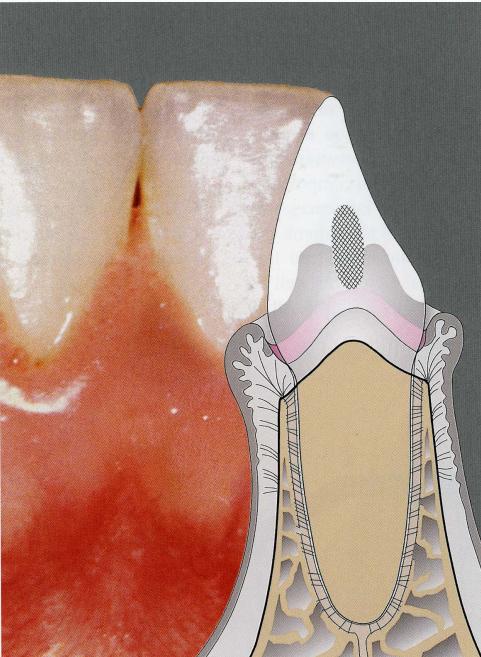


Rateitschak, et al Color Atlas of Dental Medicine, Periodontology 2nd ed

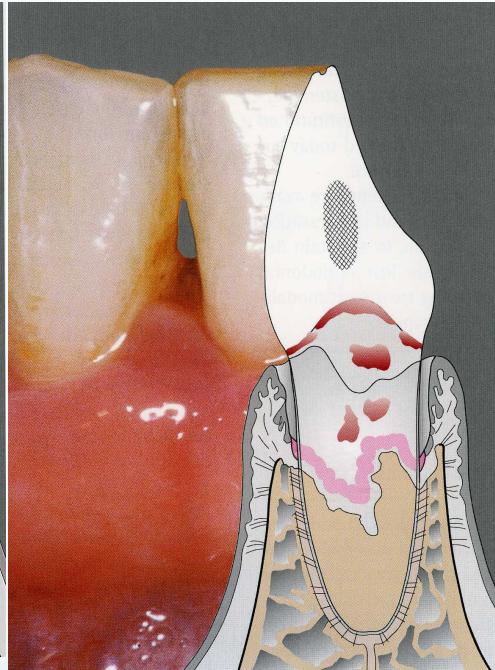
- dense LP
- gingival fibers insert \varnothing CEJ
- perio lig: bony crest to CEJ



HEALTH



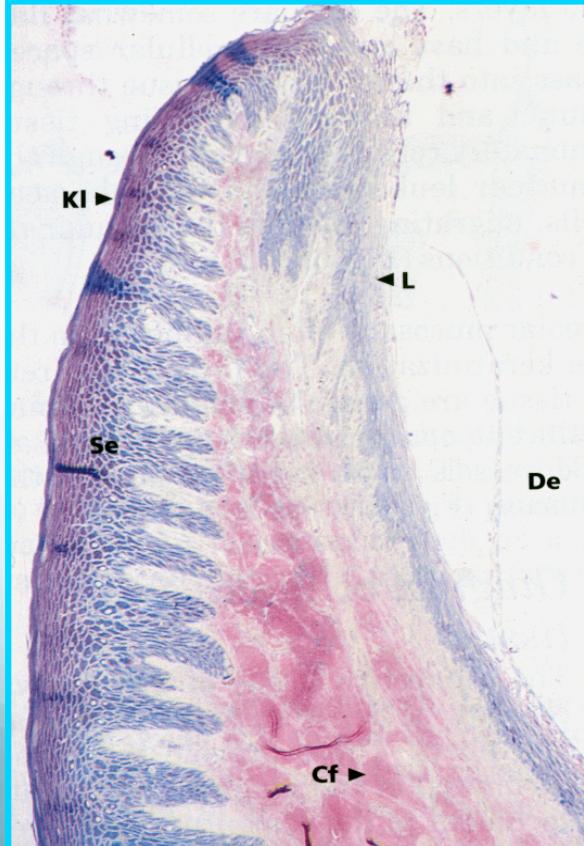
GINGIVITIS



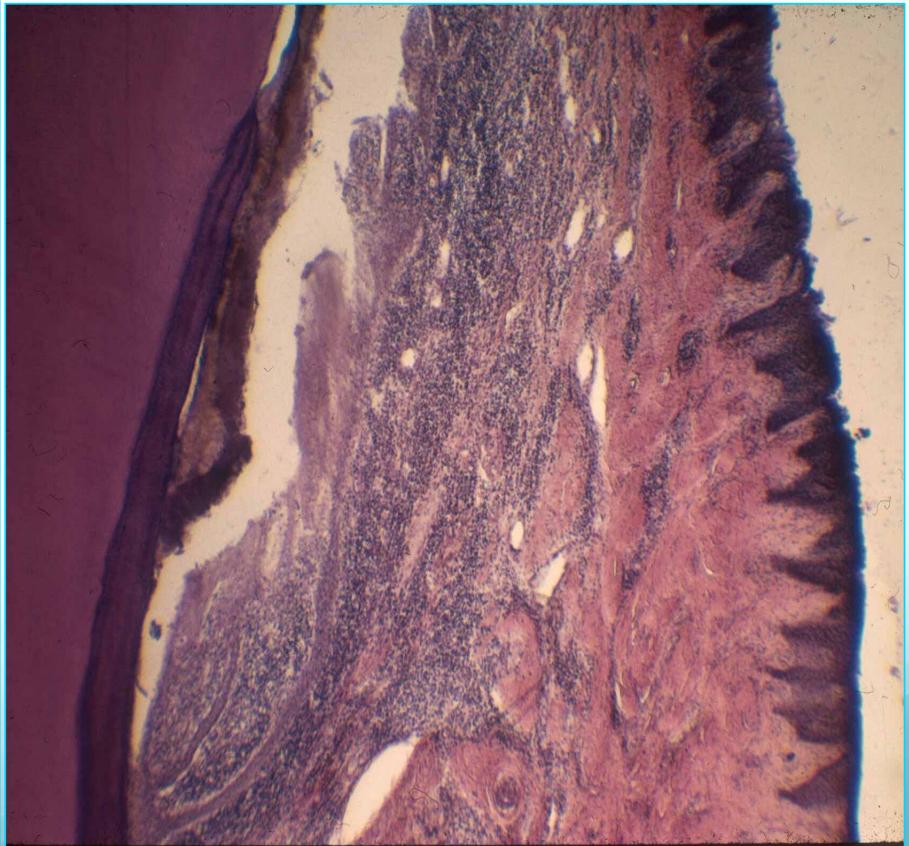
Periodontitis

Histologic Picture of Health and Periodontitis

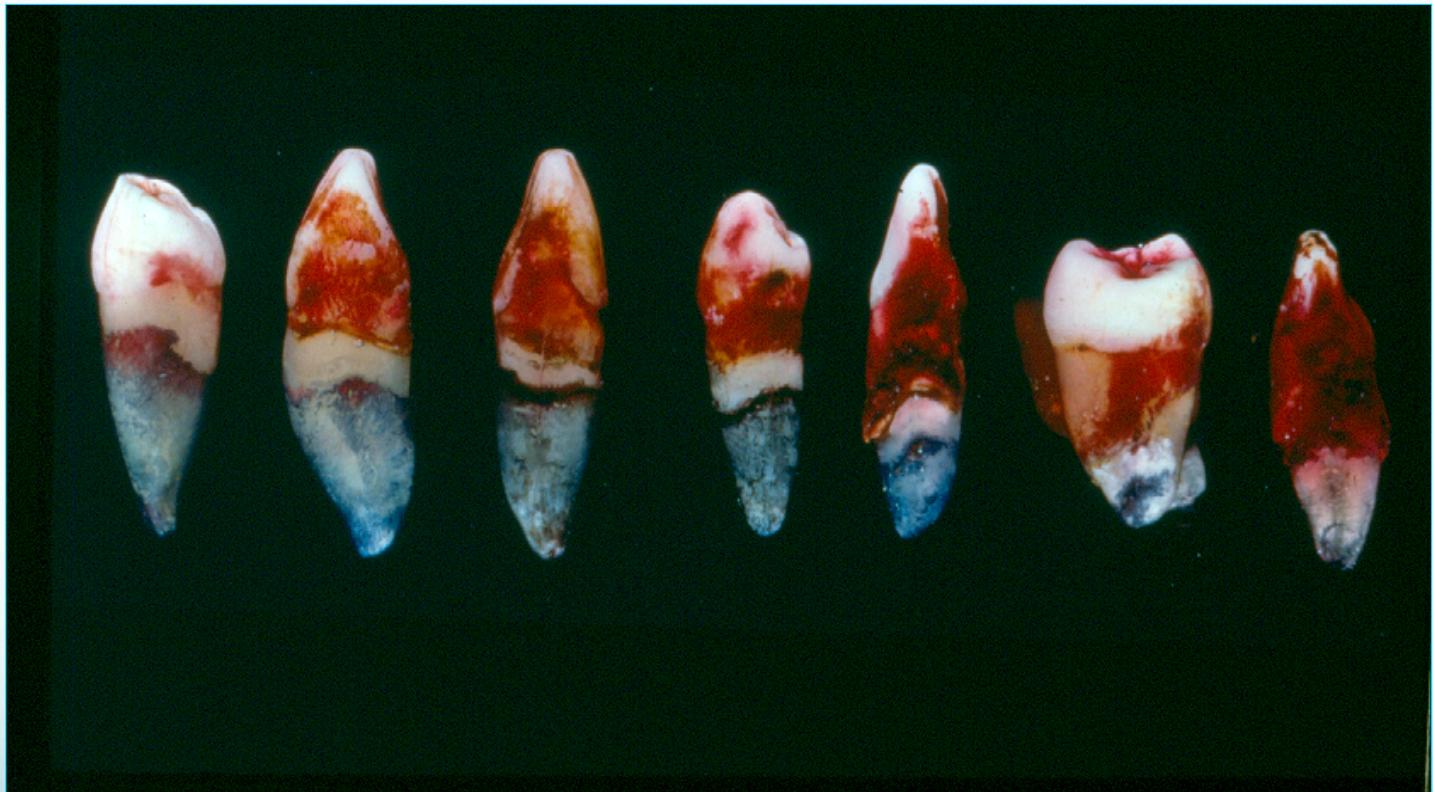
Healthy Gingival Crevice



Periodontal Pocket, Periodontitis



The progression of periodontitis



Periodontitis Lesion

- Characterized by loss of connective tissue attachment, epithelial down growth, and destruction of bone
 - Note: the body always covers exposed connective tissue with epithelium
- Presence of bacteria in the form of a complex biofilm composed of 600+ bacterial species (with gingivitis and periodontitis gm- anaerobic rods, spirochetes predominate)
- The bacteria are largely confined to the periodontal pocket at some distance from the tissue destruction

Periodontitis Lesion

- The gingival connective tissue of the established gingivitis or periodontitis lesion contains a decreased amount of collagen fibers and is replaced by large numbers of Plasma cells, B cells, T cells, Macrophage, PMN's
- This indicates that the lesion is an chronic inflammatory lesion
- Each of these cells have important roles in protection and potentially tissue destruction
- See Chapter 5, page 79, box 5-2 in Carranza's Clinical Periodontology 12th ed. And slide #16-24 in the classification of periodontal diseases presentation

Why are these cells in the gingival connective tissue?

- Phagocytes such as the PMN (neutrophil) and later the macrophage are recruited to the periodontal lesion as part of the innate host response

Why are these cells in the gingival connective tissue?

- They are recruited there by several means including:
 - **Complement activation** (alternate pathway-LPS, later by classical pathway via antibody), C5a, C3a-vasodilation, expression of molecules like I-CAM-1 (intercellular adhesion molecule-1), LFA-1 (leukocyte functional antigen-1).
 - **Toll like receptors** found on phagocytes, epithelial and endothelial cells, dendritic cells, recognize large classes of macromolecules unique to bacteria (e.g, LPS for gm-, lipoteichoic acid for gm+ and many others) this allows for activation and proliferation.
 - **Secretion of chemokines** by a wide variety if cells including epithelial cells, endothelial cells, and macrophage-CXCL8 (formerly IL-8), MIP-1 α , many others
 - **fMet-Leu-Phe (FMLP), C5a, Leukotrienes:** chemotactic for PMN, Macrophage.
 - **C5a** (also chemotactic for the B cell)

Inflammation: chronic vs. acute

- In any healing wound we have acute inflammation (PMN's) followed by chronic inflammation (macrophage, T & B lymphocytes, plasma cells), followed by repair and healing (fibroblasts, endothelial cells epithelial cells)
- For healing to occur the chronic inflammation has to resolve quickly and allow for fibroblasts, endothelial cells and epithelial cells to replace lost tissue (epithelium, blood vessels, connective tissue)

Inflammation: chronic vs. acute, cont.

- If chronic inflammation is allowed to persist then you have persistence of inflammatory cells, inflammatory cytokines and tissue destruction may result...**Friendly Fire**
- The host inflammatory response is successful in confining the plaque bacteria to the pocket but does not clear them.....teeth are in a sense external to the body
- Establishment of chronic inflammation in some people this results in tissue destruction and therefore Periodontitis, especially if the inflammation is excessive

Components of the Host Response in Periodontium

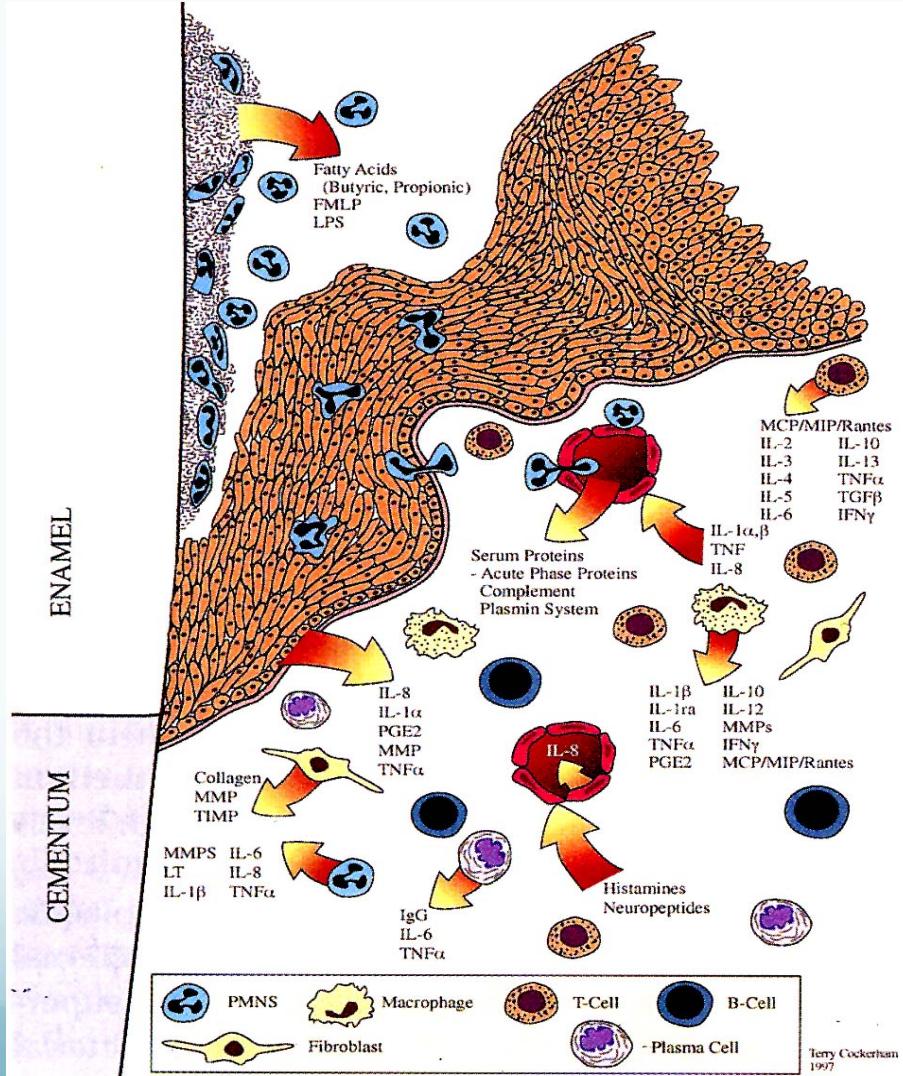
■ The innate immune system

- Acute phase response proteins (e.g., c-reactive protein)- helps with phagocytosis by facilitating complement activation
- Alternate complement pathway (C3a, C5a, C3b, etc.)
- PMNs: ROS-reactive oxygen species, acid hydrolases, elastase, proteases, collagenase=MMP-8 (MMP=matrix metalloproteinase)
- Macrophages-cytokines: IL-1 α , IL-6, IL-8, TNF- α , PGE₂ (IL=interleukin, TNF=tumor necrosis factor, PGE=prostaglandins)
- Toll-Like Receptors- found on macrophage, dendritic cells, epithelial cells endothelial cells

Key Components of the Host Response in Periodontal Tissues

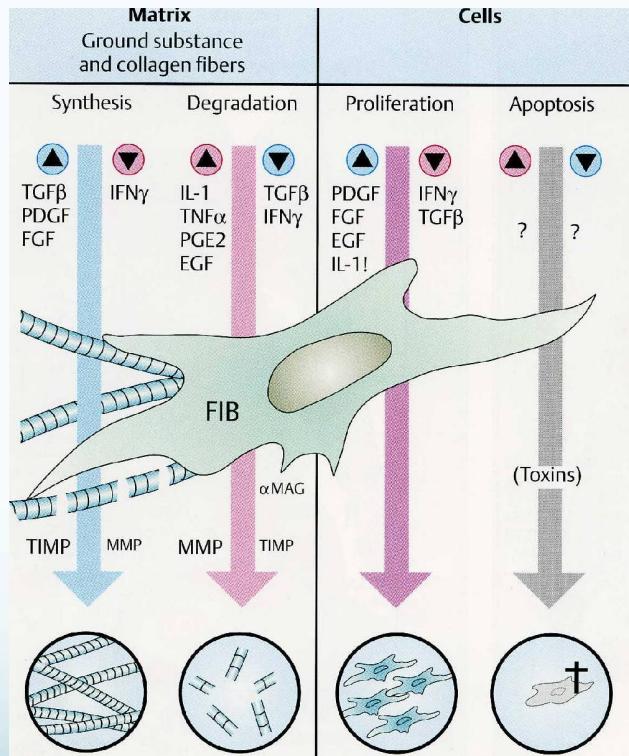
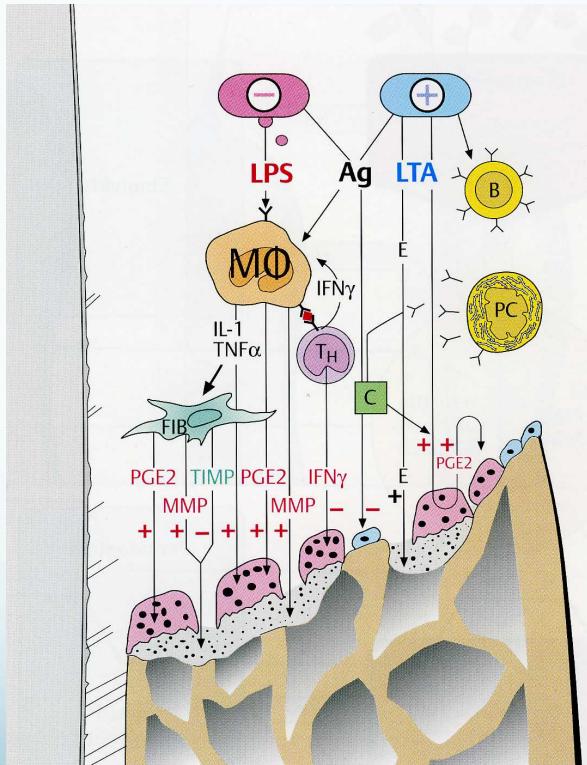
- The adaptive immune system
 - B cells (antibodies), T cells (cytokines: IFN- γ (interferon gamma), IL-2, IL-6)
 - Classical complement pathway

Inflammation, resolution, tissue destruction



The result of Innate and Adaptive Immunity

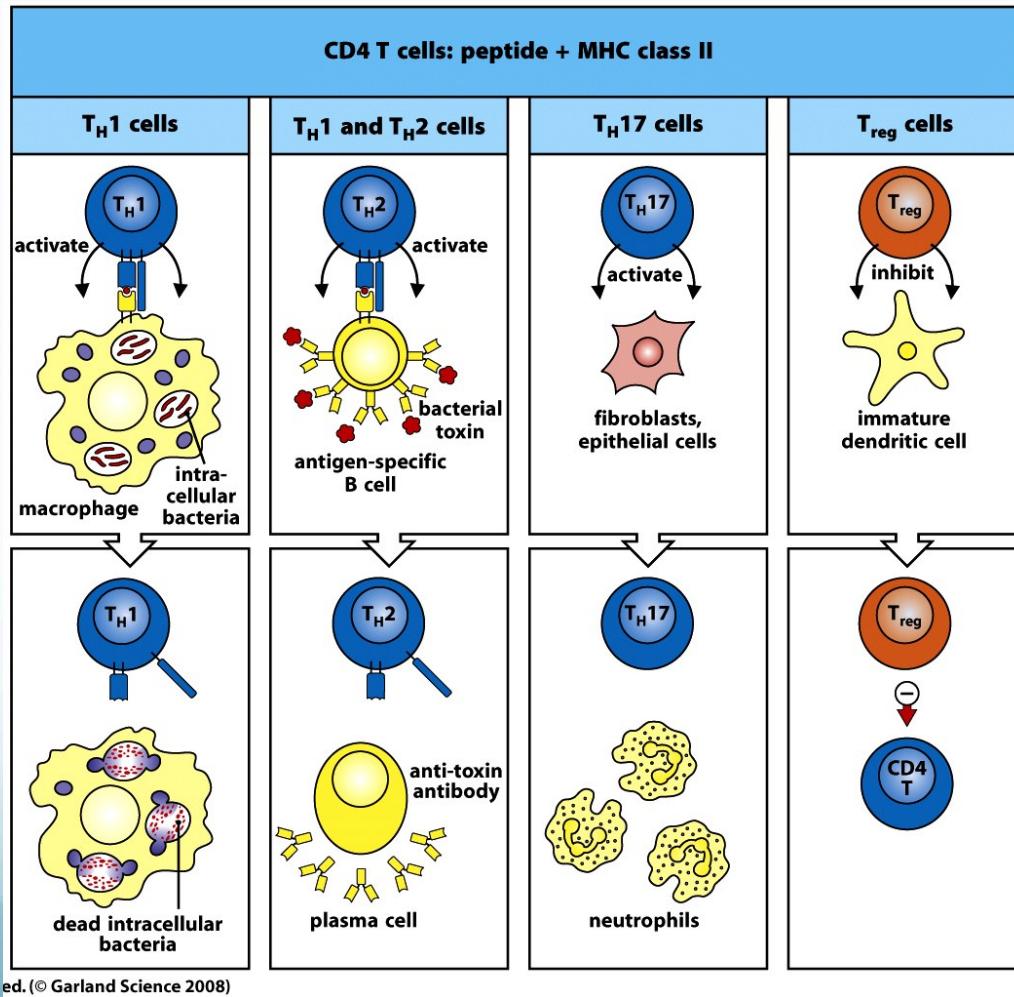
- Both together are successful in protecting the host from an invasive bacterial infection. In some people this effective host response also results in destruction of periodontal tissues.
("Friendly Fire")



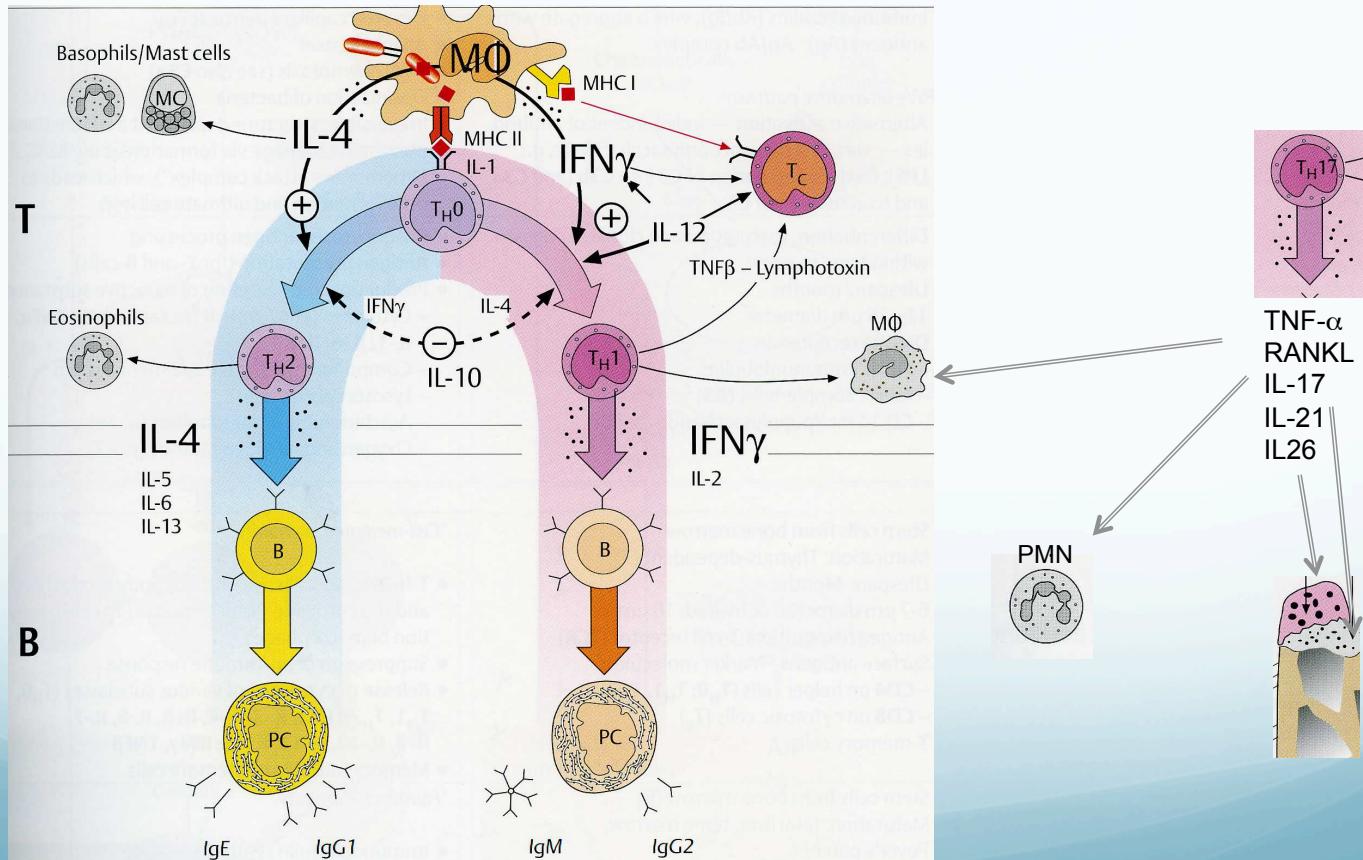
RANKL/Osteoprotegerin and the Osteoclast

- Inflammatory cytokines IL-1 β , IL-6, IL-17, TNF- α cause an increase in production of RANKL by osteoblasts, fibroblasts, and T & B cells
- RANKL (receptor activator of nuclear factor-kappa B ligand) binds its receptor (RANK) on the surface of the osteoclast, this results in an increase in bone resorption
- OPG (osteoprotogerin) is a decoy receptor that competes with RANK for binding of RANKL.
- The ratio of RANKL to OPG is more important than the absolute amount of RANKL
- Increasing the RANKL/OPG ratio increases bone resorption

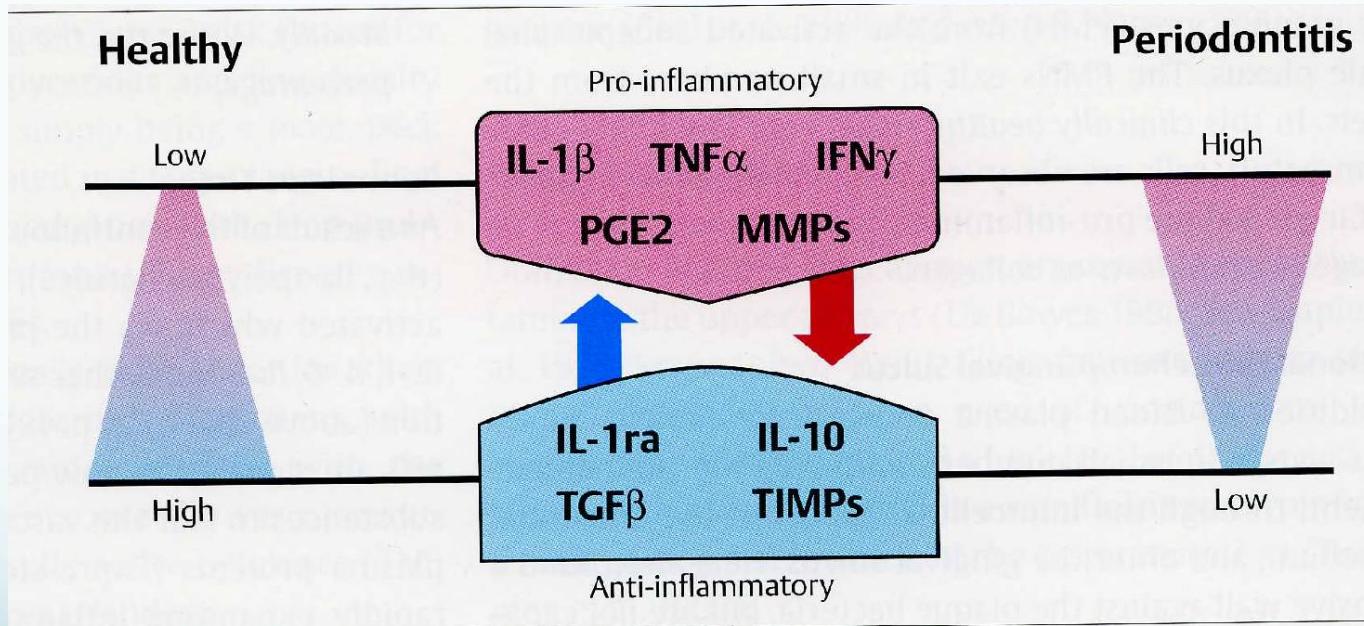
T Cells: T_H1 , T_H2 , T_H17

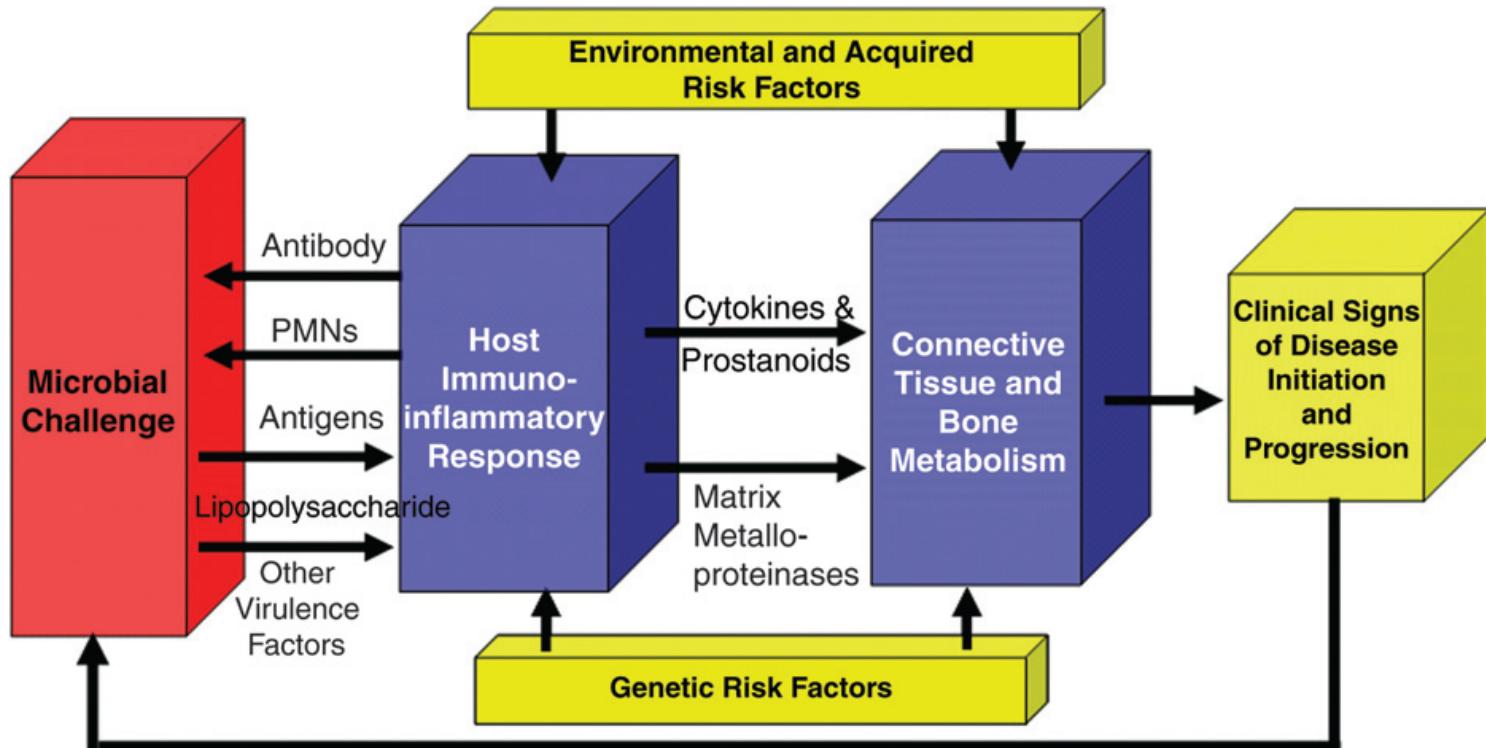


T_H1 , T_H2 , ? T_H17

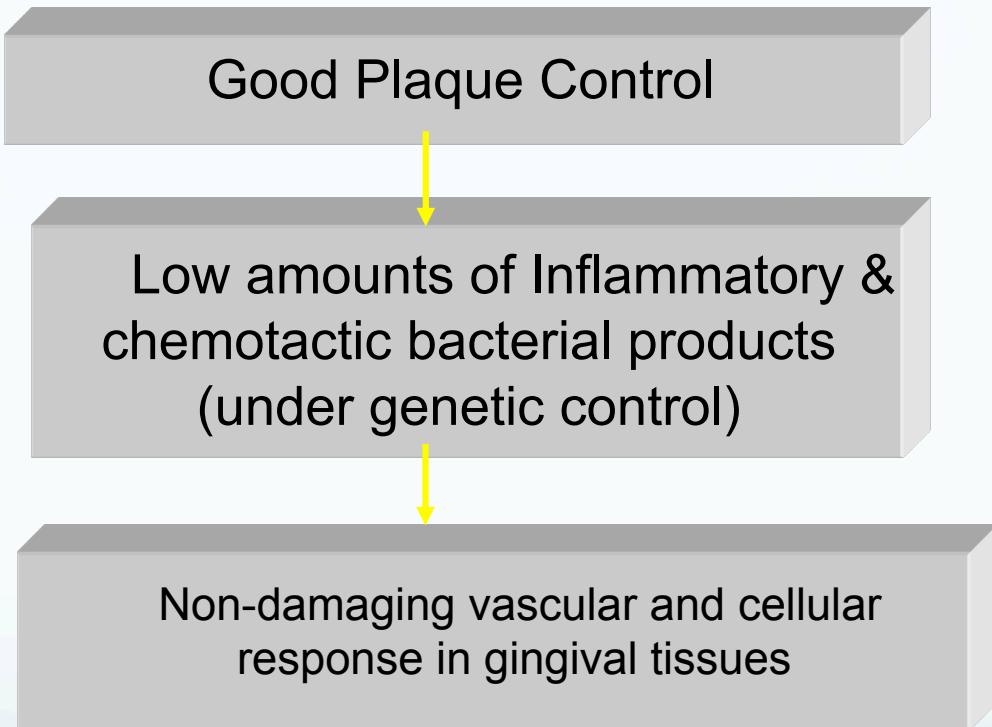


Hyperinflammatory Phenotype = periodontal tissue destruction

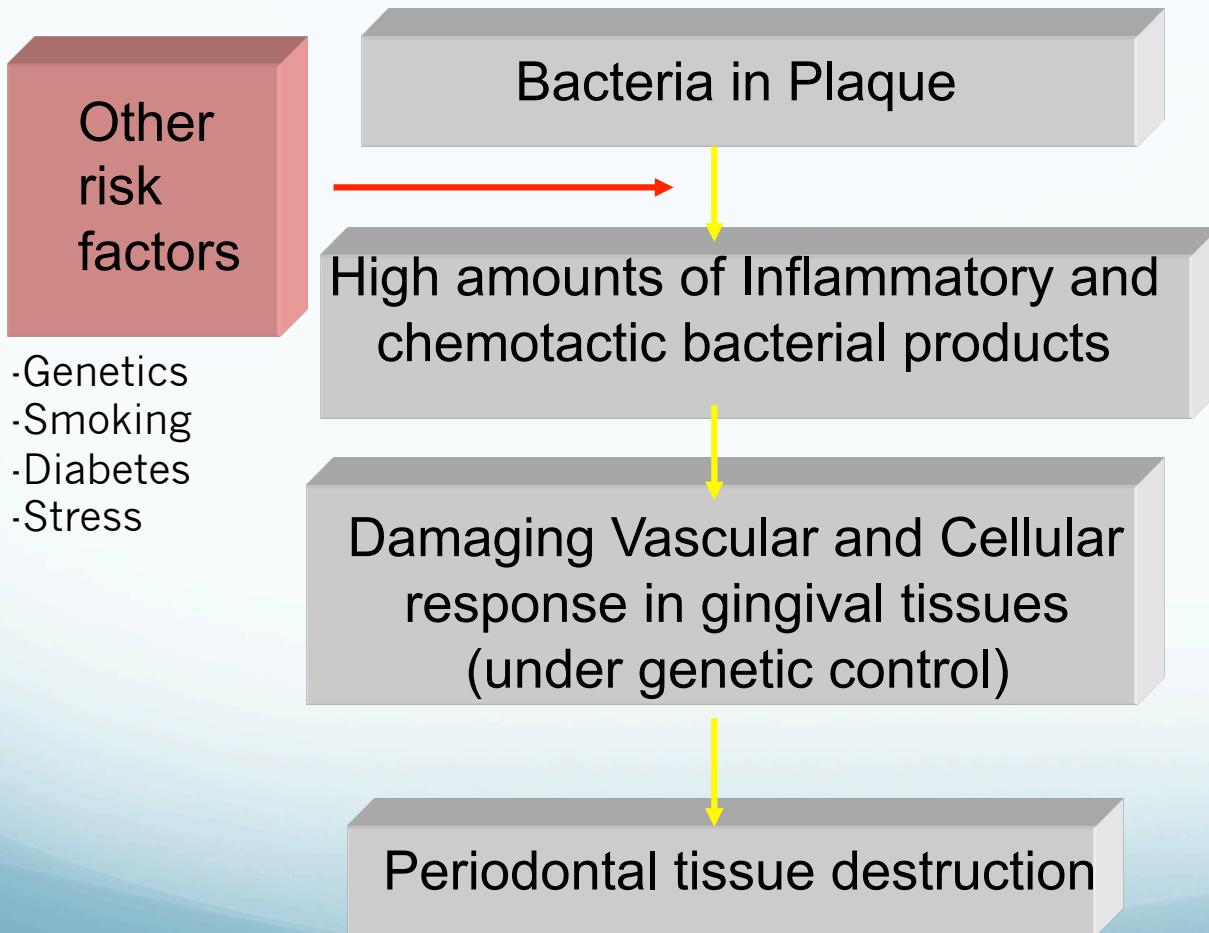




Scenario 1: the stable periodontium



Scenario 2: Active Disease



Evidence for This Model

- Protection
 - Adhesion or chemotaxis defects in PMNs and/or Macrophage/Monocyte results in severe periodontitis
 - Antibody to two periodontitis associated bacteria limit the severity of periodontal attachment loss
 - Patients with several Mendelian diseases like leukocyte adhesion deficiency (LAD), and Cyclic Neutropenia have severe periodontitis

Evidence for This Model

- Hyperinflammation
 - Most people have considerable plaque and gingival inflammation, most get only gingivitis some get periodontitis
 - Macrophage/monocytes from patients with chronic periodontitis secrete more inflammatory cytokines if stimulated with LPS *in vitro*, Genetic tendency to hyperinflammatory phenotype
 - MIP-1 α , a chemokine, persists in Papillon-Lefevre due to an absence of Cathepsin C, a protease that normally helps to break down the chemokine as PMNs accumulate in large numbers- severe periodontitis

Evidence for This Model

- Hyperinflammation
 - NSAIDs (ex. Ibuprofen, they inhibit prostaglandins like PGE₂) decrease attachment loss in patients with periodontitis
 - Resolvins and Lipoxins appear to prevent and reverse periodontitis in animal models of disease
 - Bisphosphonate drugs like Alendronate decrease bone loss by inducing apoptosis in osteoclasts

Evidence for This Model

- Hyperinflammation
 - Transplant patients and HIV infected patients (both are immunosuppressed) do not have an increased prevalence of periodontitis.
 - Periodontitis is associated with increased risk of Diabetes and CVD. These diseases likely share the same underlying genetic risk.
 - Inflammatory cytokines are also associated with these diseases
 - Foam cells in atherosclerotic plaques increase with increase IL-1- β and TNF- α
 - Insulin resistance is related directly to IL-6, CRP, TNF- α

Please read the chapter in your Carranza 12th ed Perio text!!!

- Chapter 5- Phillip Preshaw chapter is EXCELLENT!!
 - It will greatly help in you understanding of this material

Questions? Discussion

