Periodontology

First semester-Immune system and periodontal disease
Lec-11

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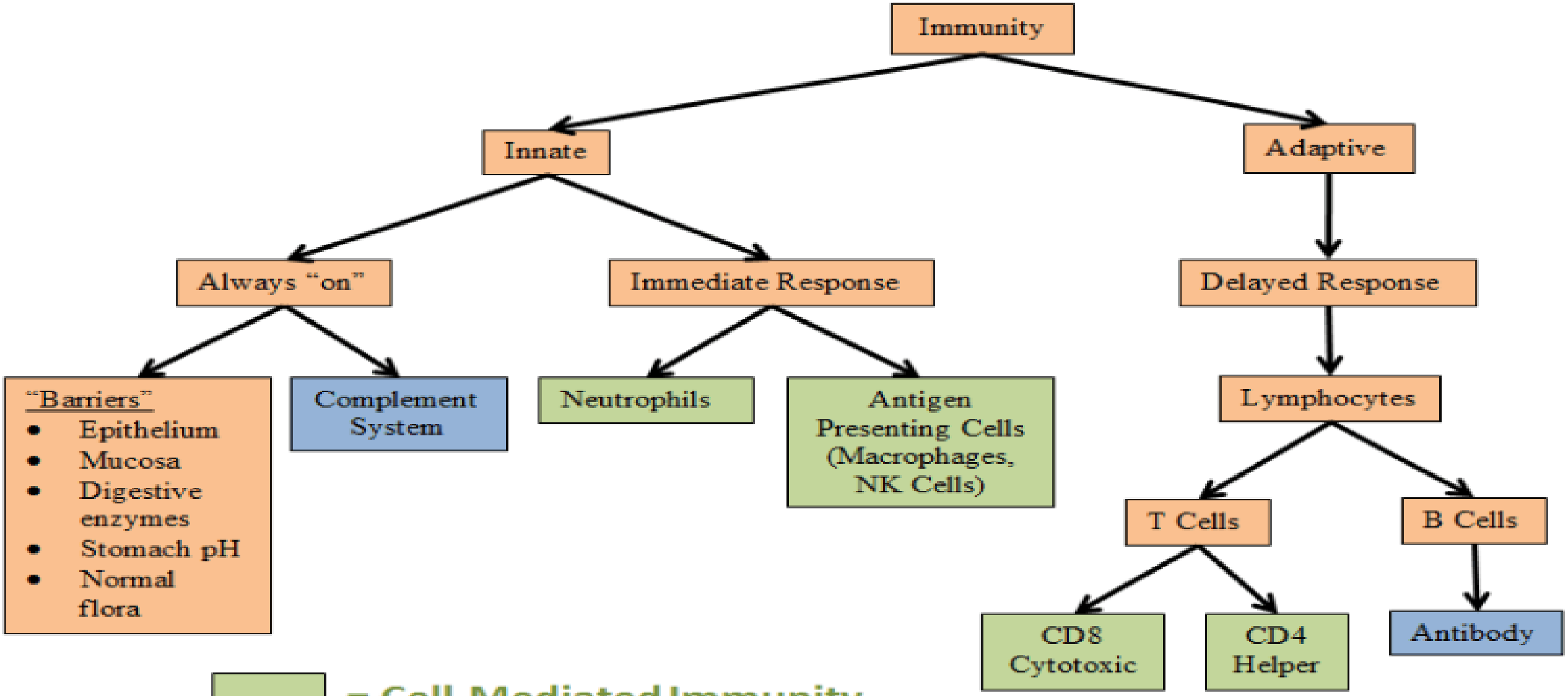
- **Immunity**: It’s the ability of the body to resist all types of organisms and toxins that tend to damage host tissues and organs.

- The host immune response may be conveniently divided into innate and adaptive immunity. Both innate and adaptive immunity operate together and not in isolation, complementing each other to maintain health and prevent disease.

- ✓ Periodontal disease is initiated by small subset of endogenous gram-negative periodontal bacteria, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans, Tannerella forsythia* and *Treponema denticola*, which trigger innate, inflammatory, and adaptive immune responses. These processes result in the destruction of the tissues surrounding and supporting the teeth, and eventually result in tissue, bone, and, finally, tooth loss.


Immunity
Innate
Adaptive
Always "on"
Immediate Response
Delayed Response
"Barriers"
Epithelium
Mucosa
Digestive enzymes
Stomach pH
Normal flora
Complement System
Neutrophils
Antigen Presenting Cells (Macrophages, NK Cells)
Lymphocytes
T Cells
B Cells
CD8 Cytotoxic
CD4 Helper
Antibody
= Cell-Mediated Immunity
= Humoral Immunity

❑ Innate immunity includes the following component parts:

- External barriers such as skin, oral mucosa, body secretions.
- Physiological factors as body pH and temperature.
- Blood and tissue leukocytes (neutrophils, monocytes, macrophages, mast cells, basophils, eosinophils and natural killer cells).
- Dendritic cells for immune surveillance and antigen presentation
- Primary and secondary lymphoid tissue
- Soluble mediators of inflammation including acute phase proteins, complement and cytokines.

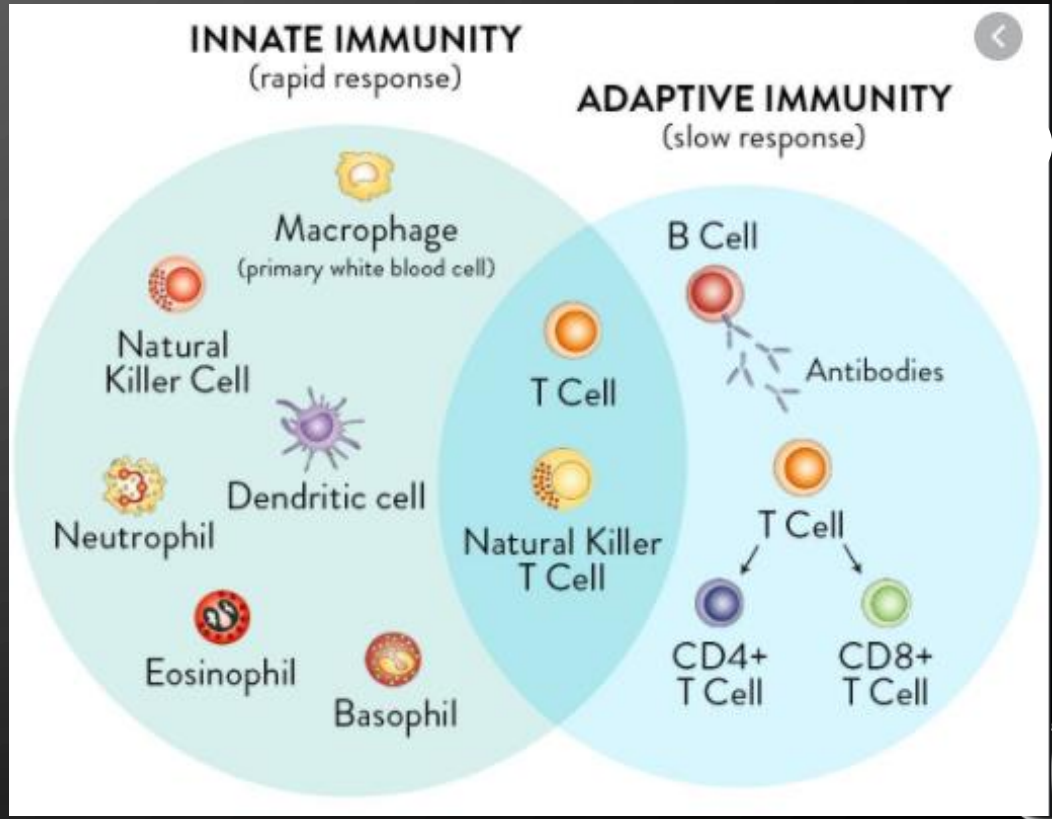
(Mills, 2013)

❑ The adaptive or acquired immune response system is mediated by:

- T and B lymphocytes which are commonly referred to as T Cells and B Cells.

- **There are three important characteristics to adaptive immunity:**

• Self-recognition (or recognition of non-self)
• Specificity
• Memory



Development of gingival inflammation

- ✓ In order to better understand the complex role of the innate and acquired immune system in the initiation and progression of periodontal disease, models of disease will be presented that utilize the four stages in the pathogenesis of inflammatory periodontal disease originally described by Page and Schroeder, Laboratory Investigation, 1976.

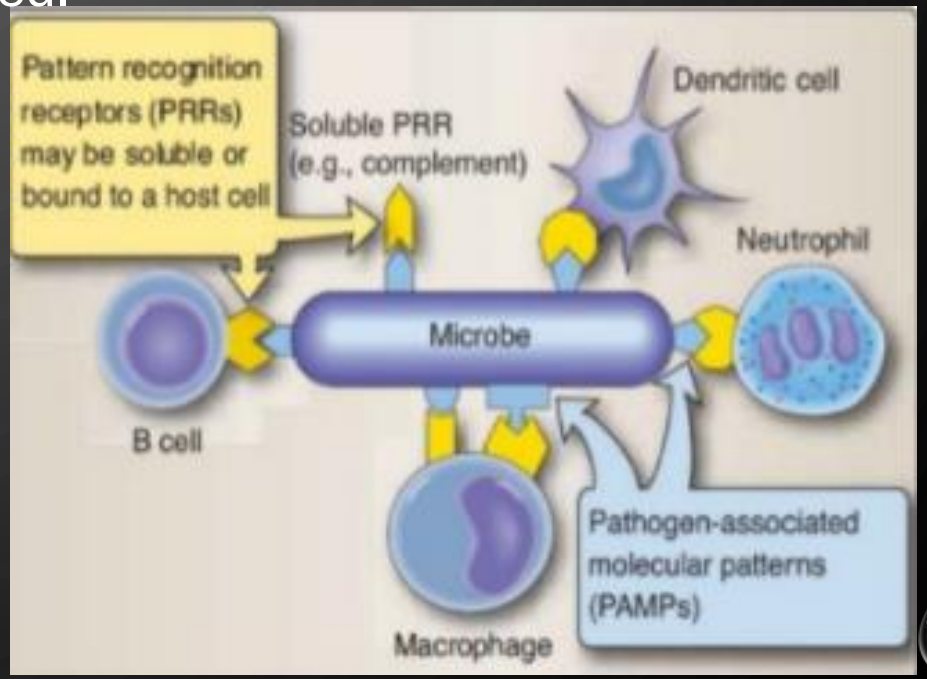
❖ Initial Lesion (2-4 days)

If a biofilm is allowed to form on the tooth surface, a vast number of bacterial cell products are produced. Many of these bacterial products and structures are referred to as Pathogen- Associated Molecular Patterns (PAMPs) and can be recognized by membrane receptors called Toll-like Receptors (TLRs).

Toll-like receptors

- TLRs are part of the innate immune system and are expressed by several different cell types including Epithelial cells, endothelial cells, fibroblasts, cementoblasts, osteoblasts, osteoclasts, dendritic cells, PMNs, macrophages and lymphocytes. When PAMPs (e.g. LPS, Peptidoglycan, bacterial flagella and pili) bind to TLRs on the cell membrane, an immune response is launched.

- The result is an inflammatory response that is initiated by the release of pro-inflammatory molecules, called cytokines, and other soluble mediators of inflammation from the cell.



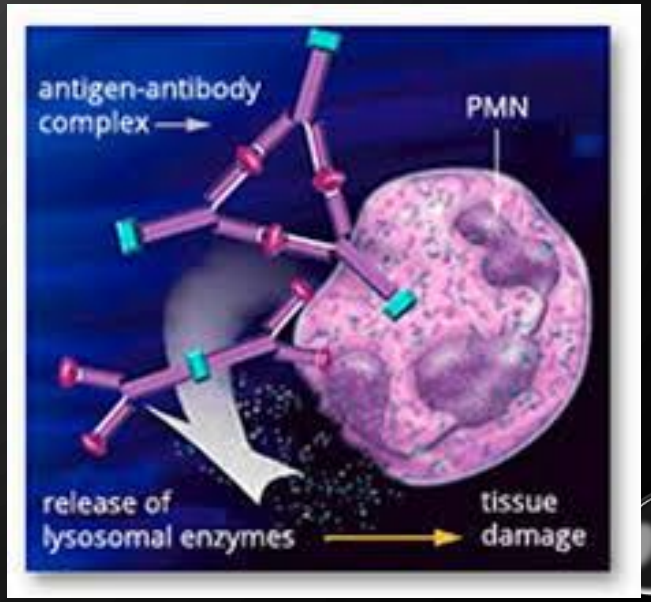
- The major pro-inflammatory cytokine is Interleukin-1 (Il-1α, Il-1β), which is released by several different cell types including sulcular/ junctional epithelium, fibroblasts, macrophages and PMNs.

- **Chemotactic cytokines or chemokines, such as Il-8, will be released which attract circulating PMNs; "the first line of defense"**

- PMNs then migrate through the vascular wall (diapedesis) and follow a concentration gradient of chemical molecules (chemotaxis) to the site of infection.

- PMNs will also migrate between junctional epithelial cells to reach the sulcus, where they literally burst and release their enzymes and also attach to antigen-antibody complexes for phagocytosis.

- PMNs and gingival fibroblasts may release enzymes called **matrix metalloproteinases (MMPs)** that are capable of breaking down extracellular matrix like collagen fibers.



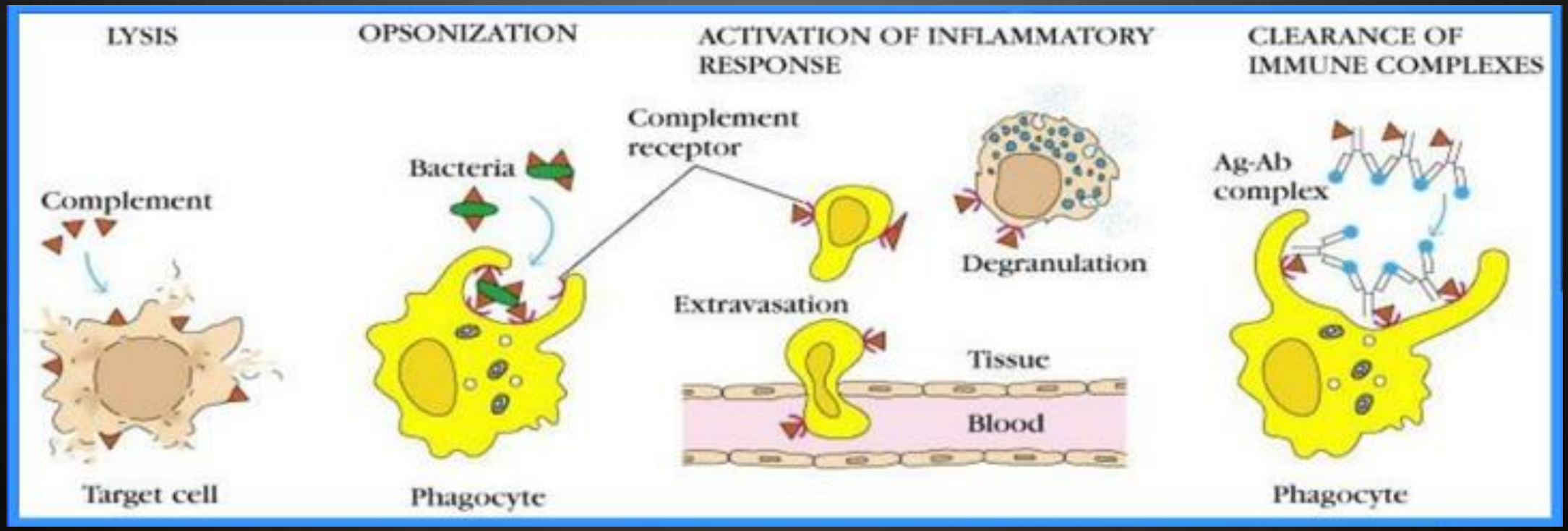
Complement system

Plasma proteins called Complement will be activated through a cascade of enzymatic reactions.

- **Complement has several biologic functions**

  - Cell lysis by MAC
  - Opsonization and phagocytosis
  - Activation of Inflammatory Response
  - Viral Neutralization
  - Removal of Immune complex

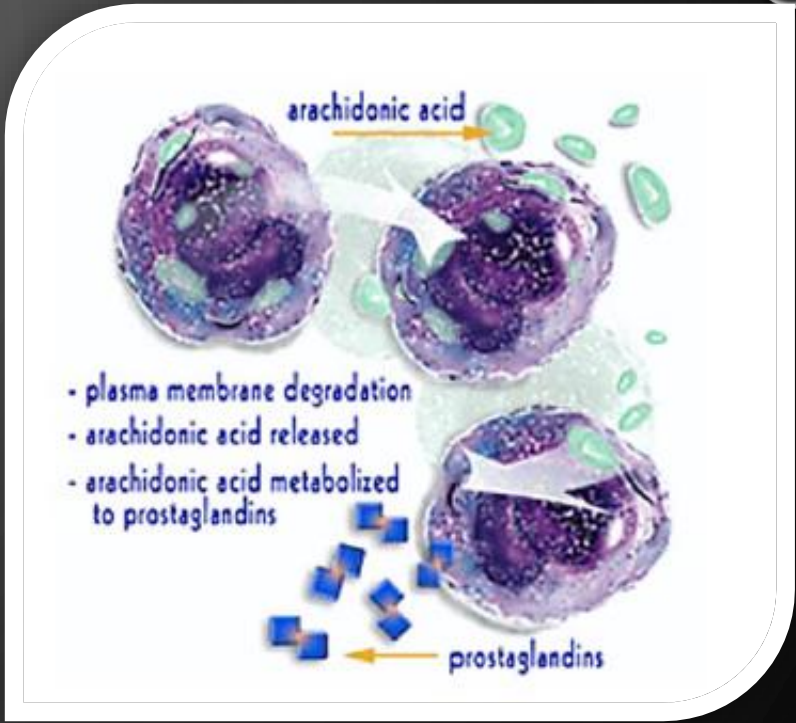
Biological functions of the Complement



✓ Prostaglandin (PG)

- IL-1 stimulate several cell to produce Prostaglandin (PG), a by-product of the enzymatic breakdown of arachidonic acid found in the lipid layer of the cell membrane.

- The prostaglandin of significance in periodontal disease is PGE2. It has been demonstrated to increase in concentration as the severity of the lesion increases.



- PG functions include platelet aggregation, vasodilation, vasoconstriction, chemotaxis of PMNs, increased vascularity and bone resorption.

- If the immune response is effective in eliminating the pathogens in the early phase of the acute inflammation, lipoxins from the enzymatic breakdown of arachidonic acid are generated.

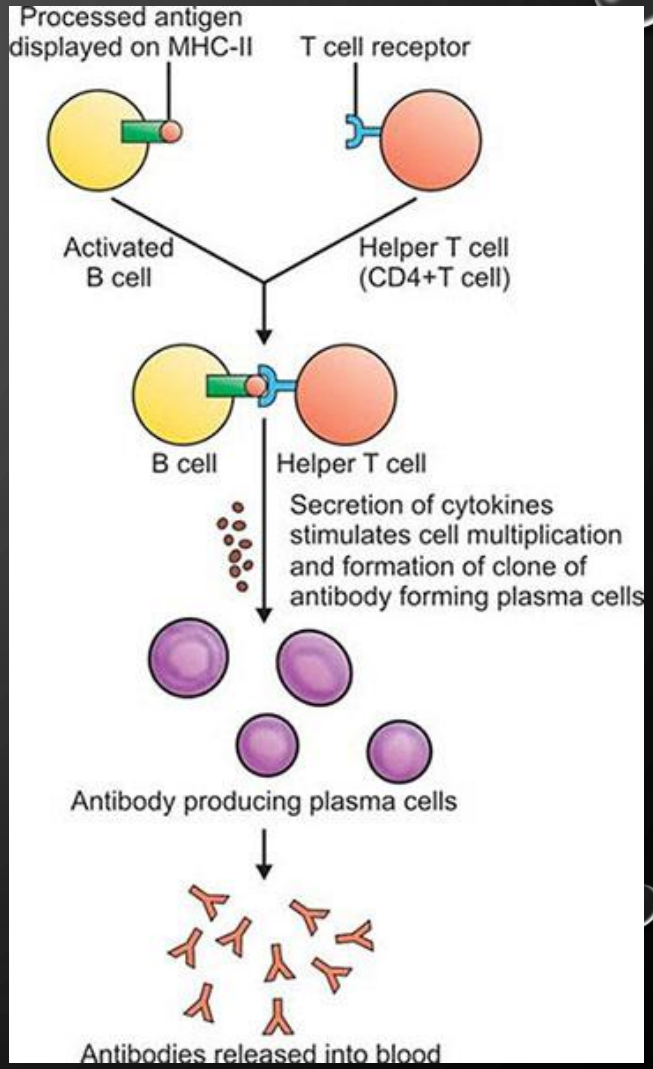
❖ Lipoxins function

- Inhibit PMN chemotaxis,
- Inhibit secretion of proinflammatory mediators,
- Induce apoptosis (cell death) of PMNs, and, recruit macrophages to the site for removal of cell debris.

❖ Early Lesion (4-7 days)

- If the pathogens have not been eliminated, the immune response will intensify. Hallmarks of the *Initial Lesion* will continue.

- Several studies have shown these small lymphocytes to be primarily T cells. Once activated by Antigen Presenting Cells such as the macrophage or dendritic cell, T Cells may function as helper and / or cytotoxic cells that orchestrate an appropriate immune response.



In a gingivitis lesion, T helper Cells

- Increase the ability of macrophages to kill intracellular and extracellular pathogens,
- Activate PMNs independently of the cytokines produced,
- Enhance PMN and macrophage phagocytosis.

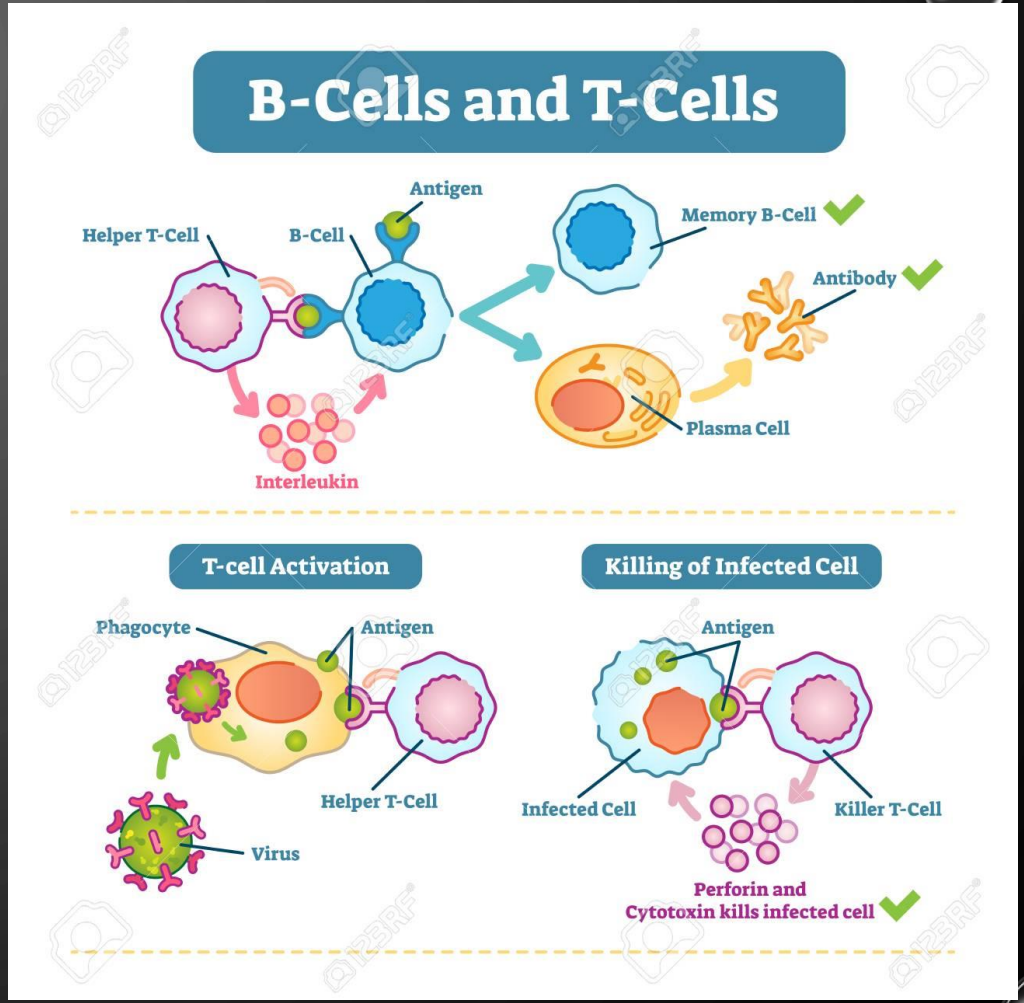
❖ Established Lesion (2-3 weeks)

- If the T Cell is unable to effectively deal with the infection and it becomes chronic, a more robust immune response may be required.

- Another significant change from earlier stages of disease is the predominance of Ig producing Plasma Cells within the inflammatory infiltrate. Thus, an increase in extravascular immunoglobulins (antibodies) can now be detected within the connective tissue and junctional epithelium. These changes may be linked to one or more immune system events.

- It is logical that B Cells have migrated to the site of infection in the Established Lesion. Some are memory B cells that have antigen specific Immunoglobulins (Ig) expressed on their surface membrane.

- ✓ Macrophage activated T helper-2 Cells (Th2).The process of activation results in proliferation and differentiation into Ig producing Plasma Cells. Immunoglobulins will subsequently be available to opsonize and neutralize the antigens.

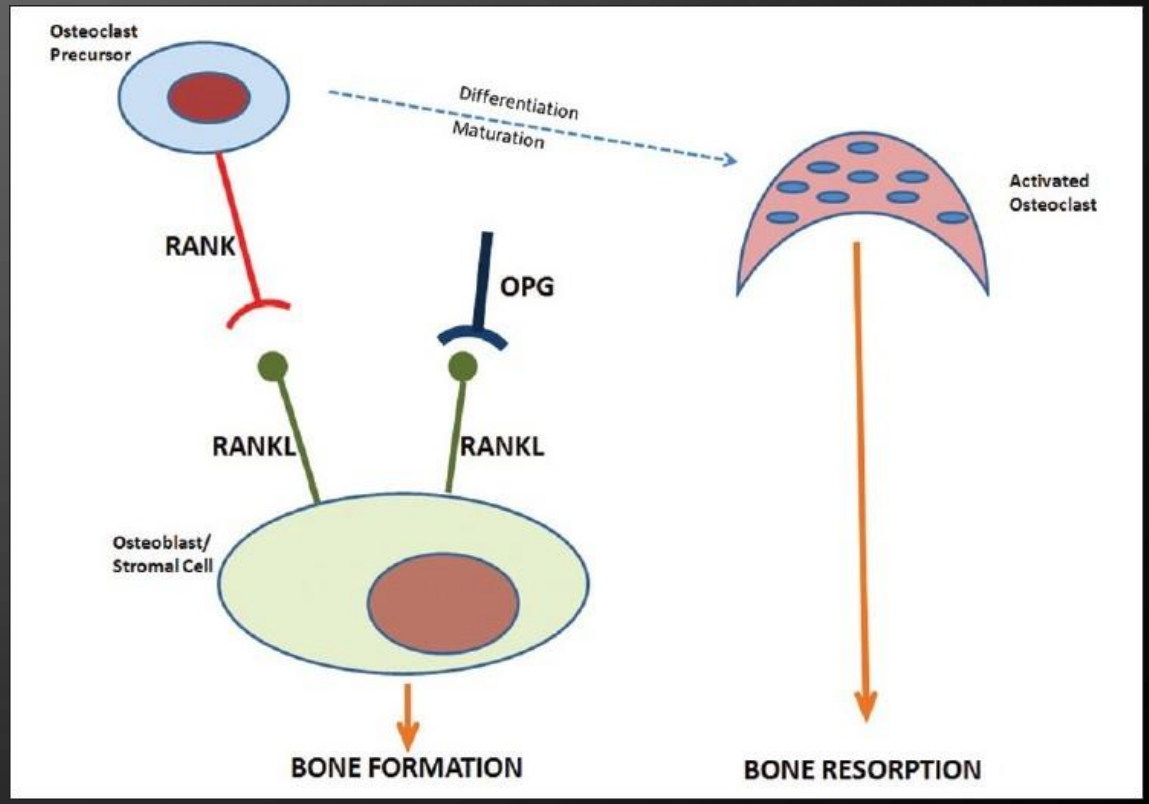


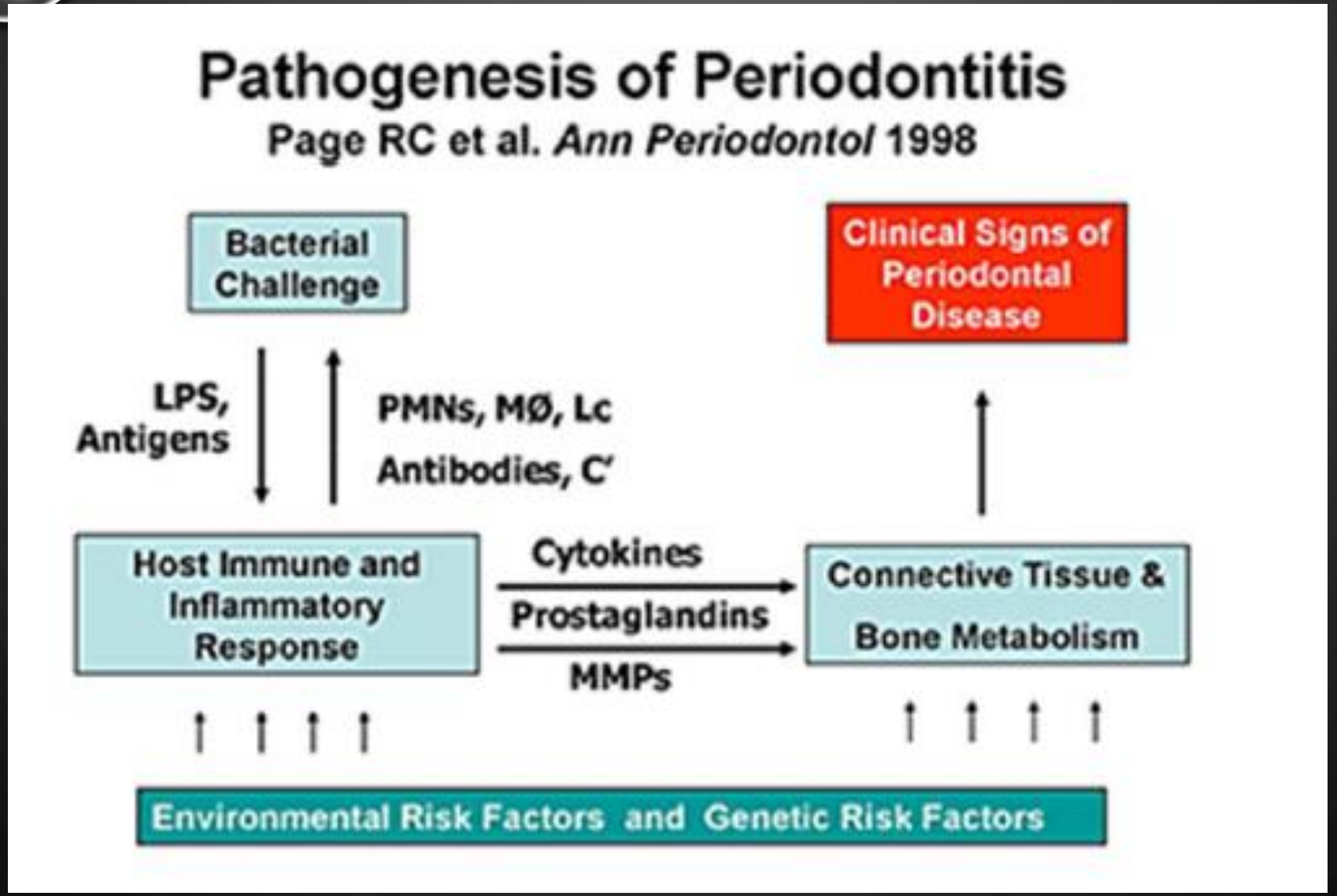
❖ Advanced Lesion

- Several of the features described for the Established Lesion will persist at this stage.
- The mediators of inflammation that have been identified as playing a significant role in alveolar bone resorption include interleukin-1β, interleukin-6, Tumor Necrosis Factor-α (TNFα), and Prostaglandin E2. Every cell involved in the immune response is capable of secreting these molecules.
- In addition, each of these mediators has been shown to increase in periodontitis sites compared to sites displaying gingivitis or health.
- The newest area of investigation involves the Receptor Activator of Nuclear Factor κB Ligand, **(RANKL)** and its decoy receptor, osteoprotegerin

- Osteoblasts express RANKL on their cell membrane. When this ligand binds to the RANKL receptor on a pre-osteoclast, it signals the cell to differentiate into an active osteoclast.

- The decoy receptor for RANKL, called osteoprotegerin, blocks this activation mechanism, thus helping to maintain bone homeostasis. In periodontitis, the ratio of RANKL to osteoprotegerin increases, whereas in health, the ratio is decreased.





The figure is a simplified model reminding us of the complex nature of periodontal disease.

Bibliography

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- *MILLS, M. P. J. D., EDUCATION COURSE 2013. Immunological and Inflammatory Aspects of Periodontal Disease. 1, 1-8.*


Thank You
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and
CHRISTOPHER
JAMES REEVES