First semester-Periodontal Disease Pathogenesis And Host-parasite interaction Lec.12,13

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- ***Pathogenesis*** refers to the processes that cause disease. In periodontitis, bacteria in the biofilm stimulate an immune–inflammatory response that causes the tissue damage that we recognize clinically as periodontitis.

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

MECHANISMS OF PATHOGENICITY

For a periodontal pathogen to cause disease, it is essential that the pathogen be able to

(1) colonize the subgingival area
(2) produce factors that either directly damage the host tissue or lead to the host tissue damaging itself.

To colonize subgingival sites, a species must be able to

(1) Attach to one or more of the available surfaces.
(2) Multiply.
(3) Compete successfully against other species.
(4) Defend itself from host defense mechanisms.

Inflammatory Responses in the Periodontium

The molecules that play a role in the pathogenesis of periodontitis can be broadly divided into two main groups:

- Those derived from the subgingival microbiota (i.e., microbial virulence factors)
- Those derived from the host immune–inflammatory response.

Virulence Factor

Two general mechanisms of pathogenesis have been hypothesized.

- The first involves invasion by subgingival species .
- The second suggests a " long rang attack where cells of the pathogenic species remain in the pocket but fragments of cells as well as other ' virulence factors enter the underlying periodontal tissues and either directly damages the tissues or cause immune pathology (indirectly)

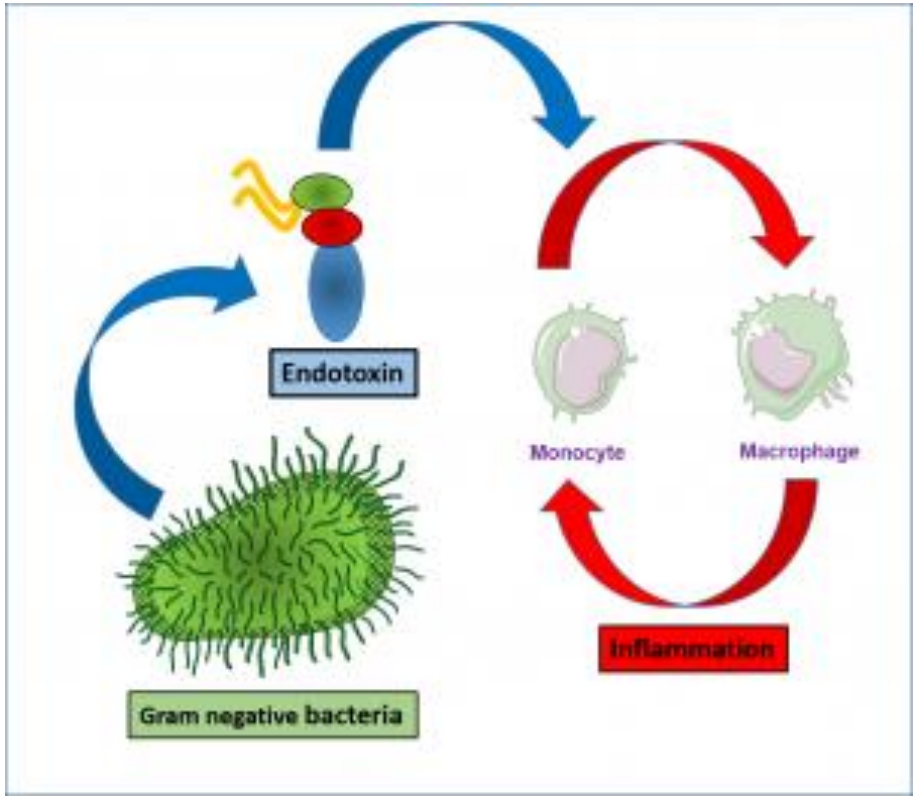
Virulence factors can be divided into three categories:

- ✓ Substances that damage tissue cells (e.g. H2S).
- ✓ Substances that cause cells to release biologically active substances (e.g. lipopolysaccharide).
- ✓ Substances that affect the intercellular matrix (e.g. collagenase).

Microbial Virulence Factors

- ***Lipopolysaccharide***

(LPS is frequently referred to as endotoxin).



- ***Bacterial Enzymes and Noxious Products***

These include noxious agents such as ammonia (NH3) and hydrogen sulfide (H2S), butyric acid are known to induce T and B cell apoptosis and influence cytokine production.

- **Fimbriae**

The fimbriae of certain bacterial species, particularly P. gingivalis, may also play a role in periodontal pathogenesis by modifying and stimulating immune responses in the periodontium .

▪ Microbial Invasion

Periodontal pathogens such as P. gingivalis and *Aggregatibacter actinomycetemcomitans* have been reported to invade the gingival tissues.

❖ Virulence Factors of *Porphyromonas gingivalis* that Interact With the Immune System

- Proteases (gingipains)
- Cell invasion capabilities
- Lipopolysaccharides
- Fimbriae
- Short-chain fatty acids

❖ *Virulence Factors of Aggregatibacter actinomycetemcomitans that Interact With the Immune System*

- Leukotoxin, kill PMNs and monocyte.
- Cytolethal distending toxin.
- Immunosuppression factors that inhabit antibody production.
- LPS(Lipopolysaccharide).
- Surface antigens.
- Heat shock proteins.
- Inhibition of PMNs function.

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

Cytokines

Prostaglandins

Matrix metalloproteinases (MMPs)

Inflammatory Mediators in Periodontitis

Cytokines

Cytokine are soluble protein secreted by cells which act as messenger molecules that transmit signals to other cells

- **There are pro-inflammatory and anti-inflammatory cytokines**.
- A key pro-inflammatory cytokine is interleukin-1β, which up-regulates inflammatory responses and is produced by multiple cell types in the periodontium
- Cytokine stimulate bone resorption and inhibit bone formation.

Chemokines

Chemokines are cytokine-like molecules that are characterized by their chemotactic activity, among which the most famous and best characterized is interleukin8,which has a powerful chemotactic functions for leukocytes particularly for neutrophils but also for lymphocytes and macrophages.

Lymphocyte signaling cytokines

- T helper cells are lymphocytes within the tissues which regulate both the humoral and cell mediated immune responses via cytokines.

- The humoral immune response is promoted by a T helper cell type 2 (TH - 2) which produces characteristic cytokines namely IL - 5 , IL - 10 and IL - 13 . The TH-1 lymphocytes release IL-2 and interferon (IFN) -y which enhance cell mediated responses. These cytokines provide a precise mechanism for the control of the immune response so that a sufficient response is produced to deal with the offending pathogen.

- Cytokines can influence the immune response through determining the class of immunoglobulin being produced, which may have quite a profound effect on antibody function. For example IgM molecules are more effective at bacteriolysis and IgG molecules are more effective at opsonization. The IgG antibodies exist as four distinct subclasses (IgG1, IgG2, IgG3 and IgG4) based on differences in the Fc portion of these molecules. The antibody subclass influences antibody function , IgG2 being less strong in binding antigen than IgGI . Several researchers have found IgG2 to be elevated over IgGI in patients with severe periodontitis and propose that IgG subclass levels are important factors in susceptibility to periodontitis.

Prostaglandins

- Prostaglandin E_2 (PGE_2) is a key inflammatory mediator, stimulating production of other inflammatory mediators and cytokine production.
- PGE_2 also stimulates bone resorption and plays a key role in periodontitis progression.

Matrix metalloproteinases (MMPs)

- 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.

Clinically Healthy Gingival Tissues

- To understand periodontal pathogenesis better, it is important to have an appreciation of the histology of clinically healthy tissues, as well as of inflamed gingival and periodontal tissues
- Clinically healthy gingival tissues appear **pink**, are **not swollen or inflamed**, and are **firmly attached to the underlying tooth and bone**, with **minimal bleeding on probing.**
- The dentogingival junction is a unique anatomic feature that functions to attach the gingiva to the tooth

Dento-gingival junction

Epithelial portion

Connective tissue portion

Both of which are of fundamental importance for periodontal pathogenesis

Epithelial structures

- Gingival epithelium
- Sulcular epithelium
- Junctional epithelium

HISTOPATHOLOGICAL CLASSIFICATION OF PERIODENTAL DISEASE

1. INITIAL LESION
2. EARLY LESION
3. ESTABLISHED LESION
4. ADVANCED LESION

Histopathology of Gingivitis and Periodontitis

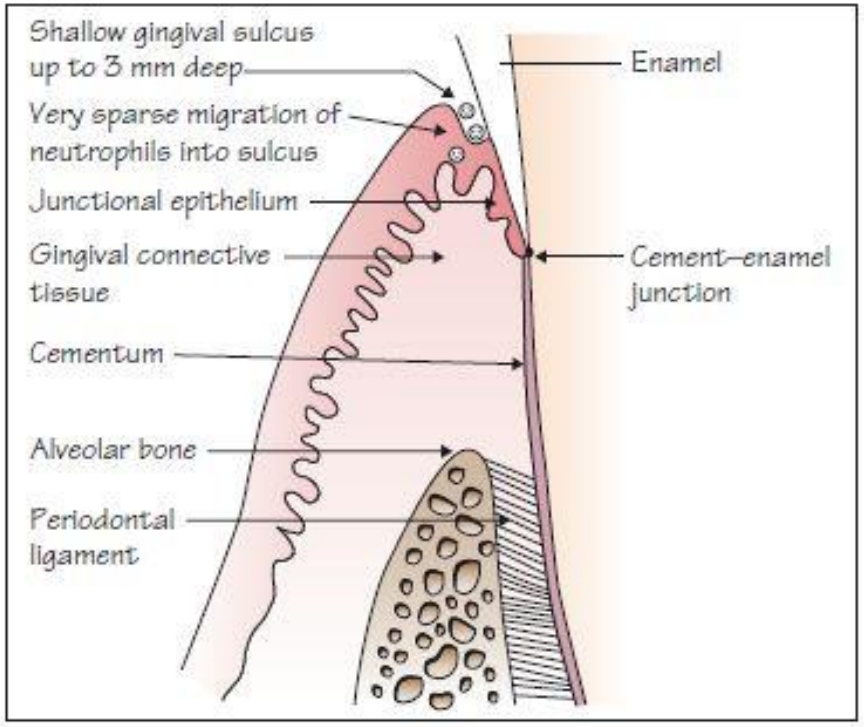
❑Stage I Gingival Inflammation: The Initial Lesion

(Corresponds With Clinically Healthy Gingival Tissues)

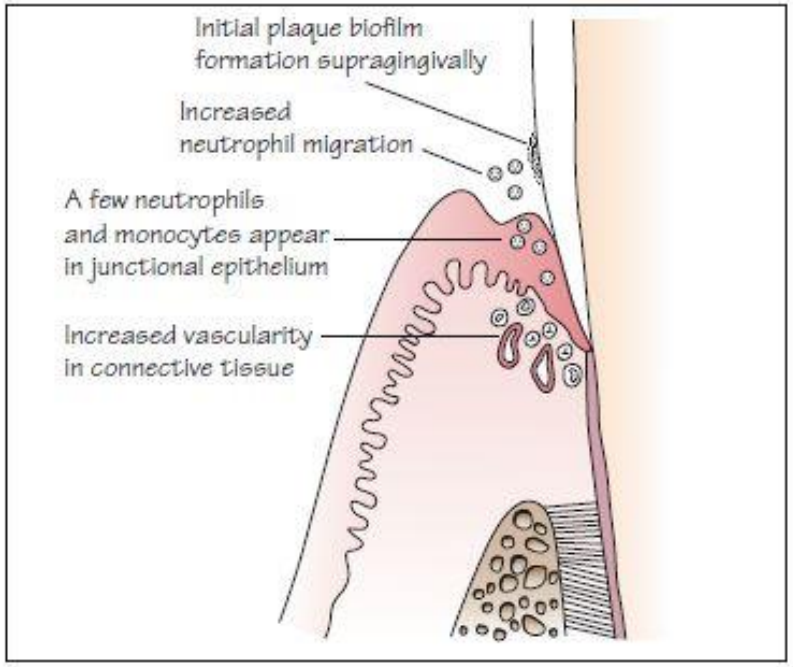
- The initial lesion was reported to develop within 2 to 4 days of the accumulation of plaque.

❑Key Features of the Histological changes

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



Normal Gingival



Stage – 1 Initial lesion

❑Stage II Gingival Inflammation: The Early Lesion

(Corresponds With Early Gingivitis. That Is Evident Clinically)

✓ The early lesion evolves from the initial lesion within about 1 week after the beginning of plaque accumulation.

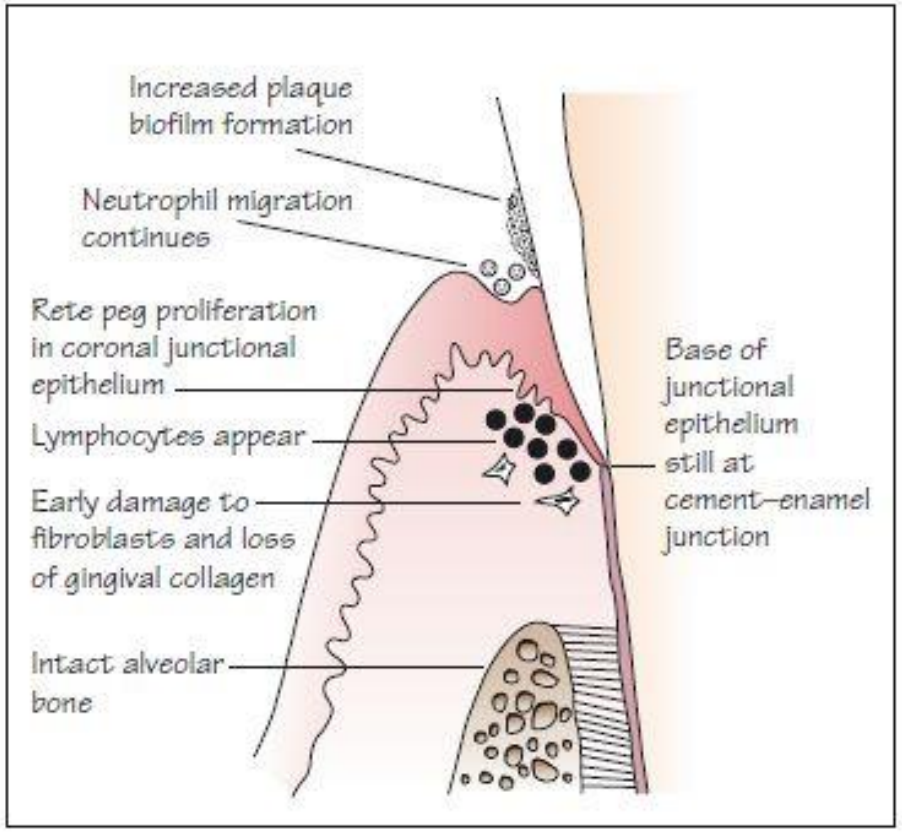
❑Key Features of the Histological changes

- Increased vascular permeability, vasodilation, and gingival crevicular fluid flow.
- Large numbers of infiltrating leukocytes (mainly neutrophils and lymphocytes).

3. Degeneration of fibroblasts.

4. Collagen destruction that results in collagen-depleted areas of the connective tissue.

5. Proliferation of the junctional and sulcular epithelium into collagen-depleted areas.



Early Lesion

❑ Stage III Gingival Inflammation: The Established Lesion

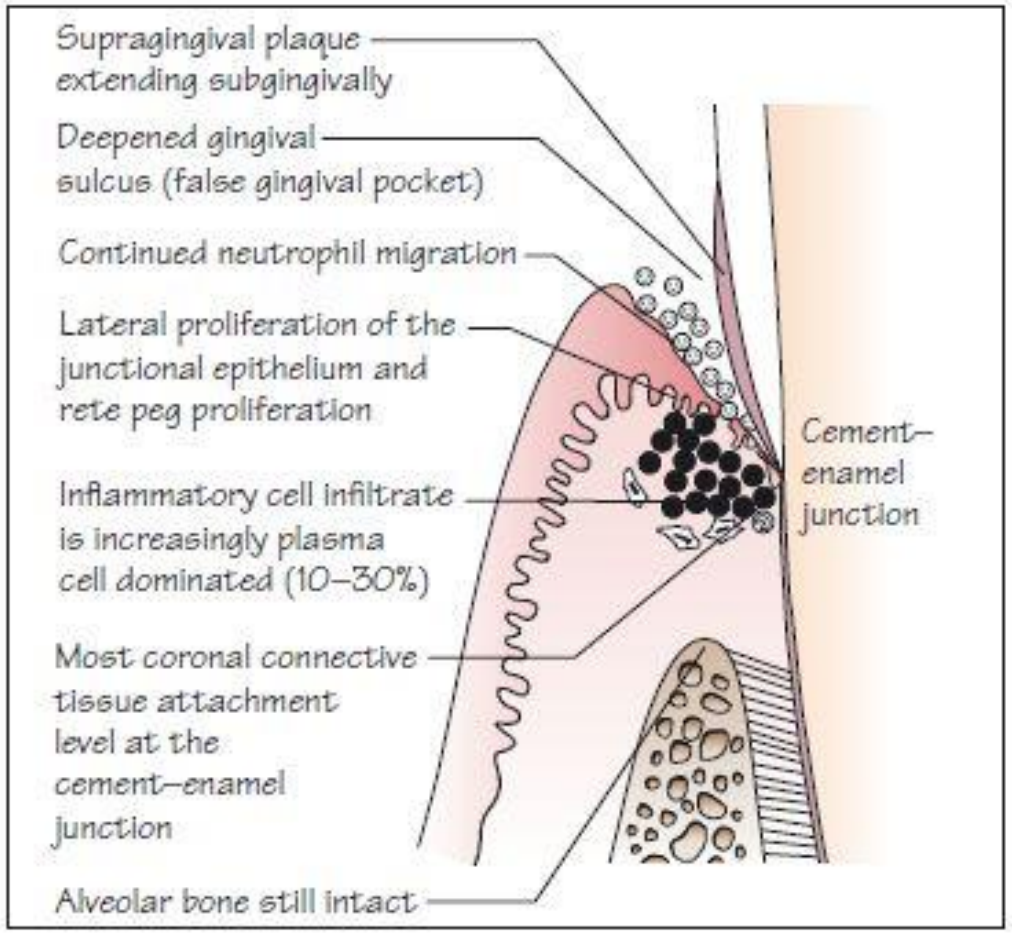
(Corresponds With Established Chronic Gingivitis)

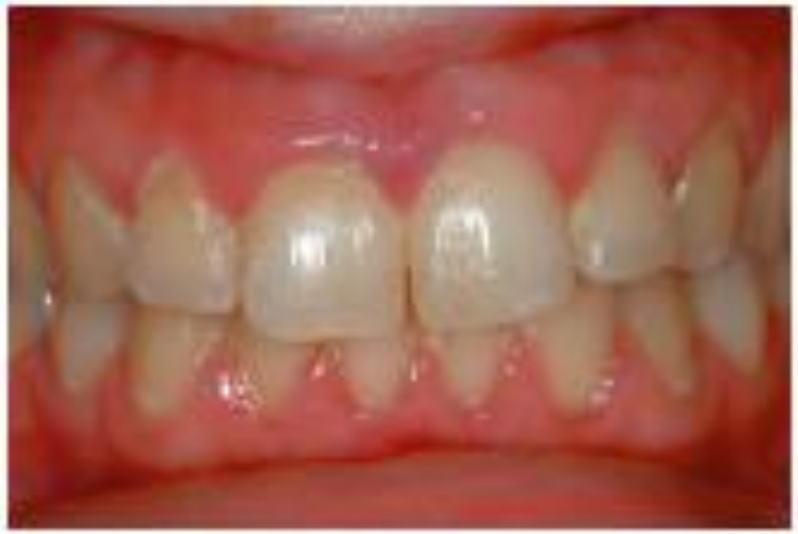
- The established lesion roughly corresponds to what clinicians would refer to as "**chronic gingivitis**, which occurs 2 to 3 weeks after the beginning of plaque accumulation.

- The progression from the early lesion to the established lesion depends on many factors, including the plaque challenge (the composition and quantity of the biofilm), host susceptibility factors, and risk factors (both local and systemic)

Key Features of the Histological changes

1. Dense inflammatory cell infiltrate (i.e., plasma cells, lymphocytes, and neutrophils).
2. Accumulation of inflammatory cells in the connective tissues.
3. Elevated release of matrix metalloproteinases and lysosomal contents from neutrophils.
4. Significant collagen depletion and proliferation of epithelium.





Established Lesion

❑Stage IV Gingival Inflammation: The Advanced Lesion

(Marks the Transition From Gingivitis to Periodontitis)

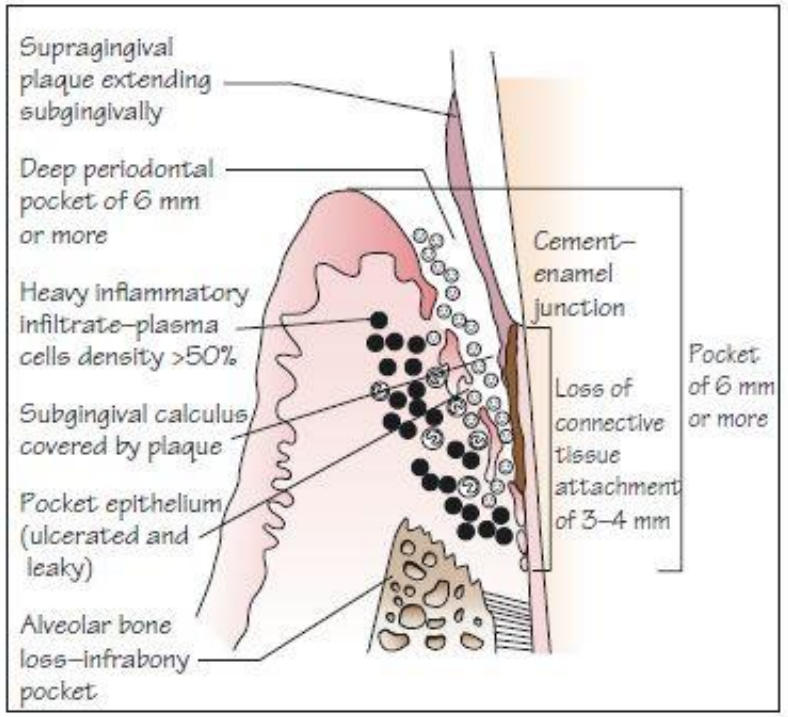
- The extension of the lesion into alveolar bone characterizes the fourth stage, which is known as the advanced lesion or phase of periodontal breakdown.

- This transition is determined by many factors, the relative importance of which is currently unknown but which includes the bacterial challenge (both the composition and the quantity of the biofilm), the host inflammatory response and susceptibility factors, including environmental and genetic risk factors.

- The advanced lesion has essentially the same cellular make-up and features as the established lesion. The main difference lies in the overt loss of attachment that is evident clinically and histologically.

❑Key Features of the Histological changes

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

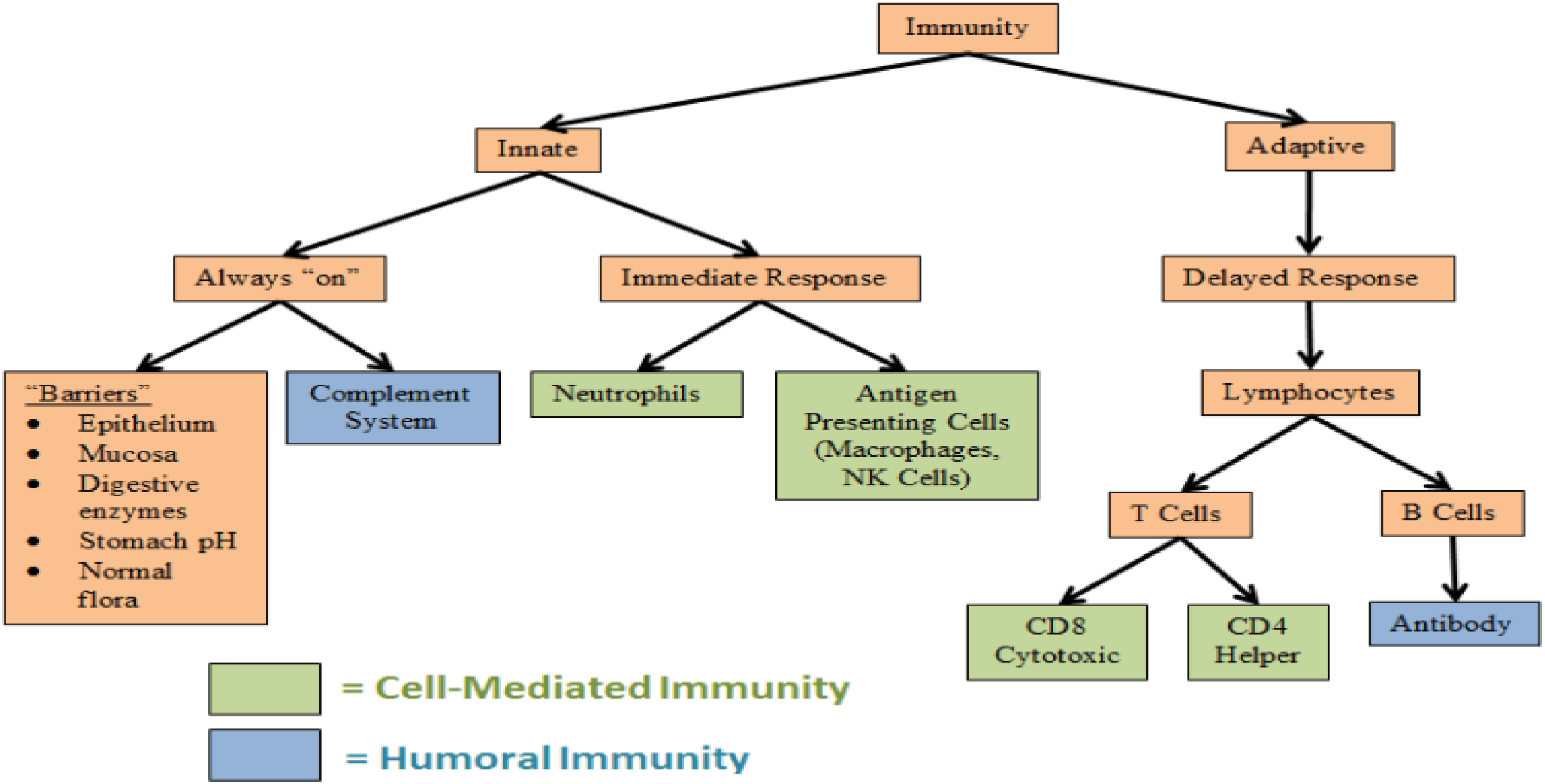


Immune Responses in Periodontal Pathogenesis

Host –parasite interactions can be divided into innate (non specific) and adaptive (specific) responses.

Innate Immunity

The first line of defense against non-self pathogens is the innate, or non-specific, immune response. The innate immune response consists of physical, chemical and cellular defenses against pathogens.



❑ 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)

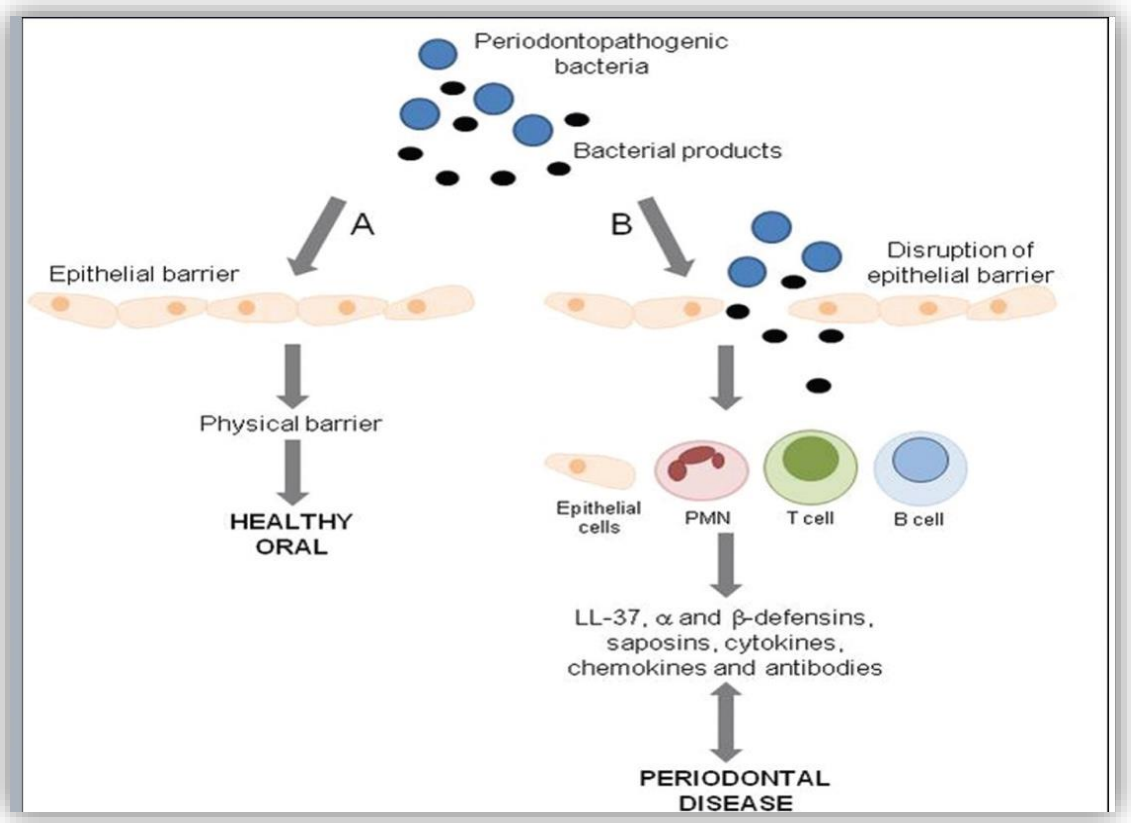
Saliva, GCF, and the epithelial keratinocytes of the oral mucosa all protect the underlying tissues of the oral cavity and the periodontium.

Constituents of Saliva that Contribute to Innate Immunity

Saliva Constituent	Host Defense Function
Antibodies (e.g., immunoglobulin A)	Inhibit bacterial adherence, promote agglutination
Histatins	Neutralize lipopolysaccharides, 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

- The keratinized epithelium of the sulcular and gingival epithelial tissues provides protection for the underlying periodontal tissue in addition to acting as a barrier against bacteria and their products.

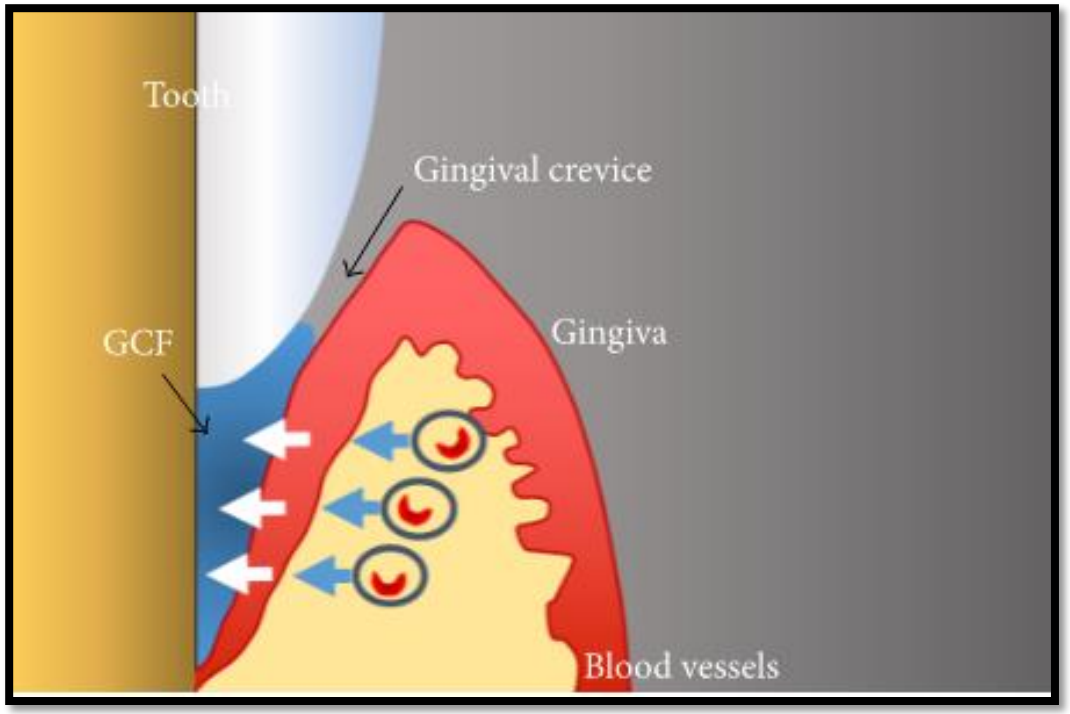
- By contrast, the junctional epithelium has significant intercellular spaces, it is not keratinized, and it exhibits a higher cellular turnover rate.



❖ **Epithelial cells also secrete a range of cytokines in response to periodontal bacteria (e.g., *P. gingivalis, A. actinomycetemcomitans, F. nucleatum, Prevotella intermedia*), which signal immune responses.**

Gingival Crevicular Fluid

It has a flushing action in the gingival crevice, but it also likely functions to bring the blood components (e.g., neutrophils, antibodies, complement components) of the host defenses into the sulcus.



Adaptive Immunity

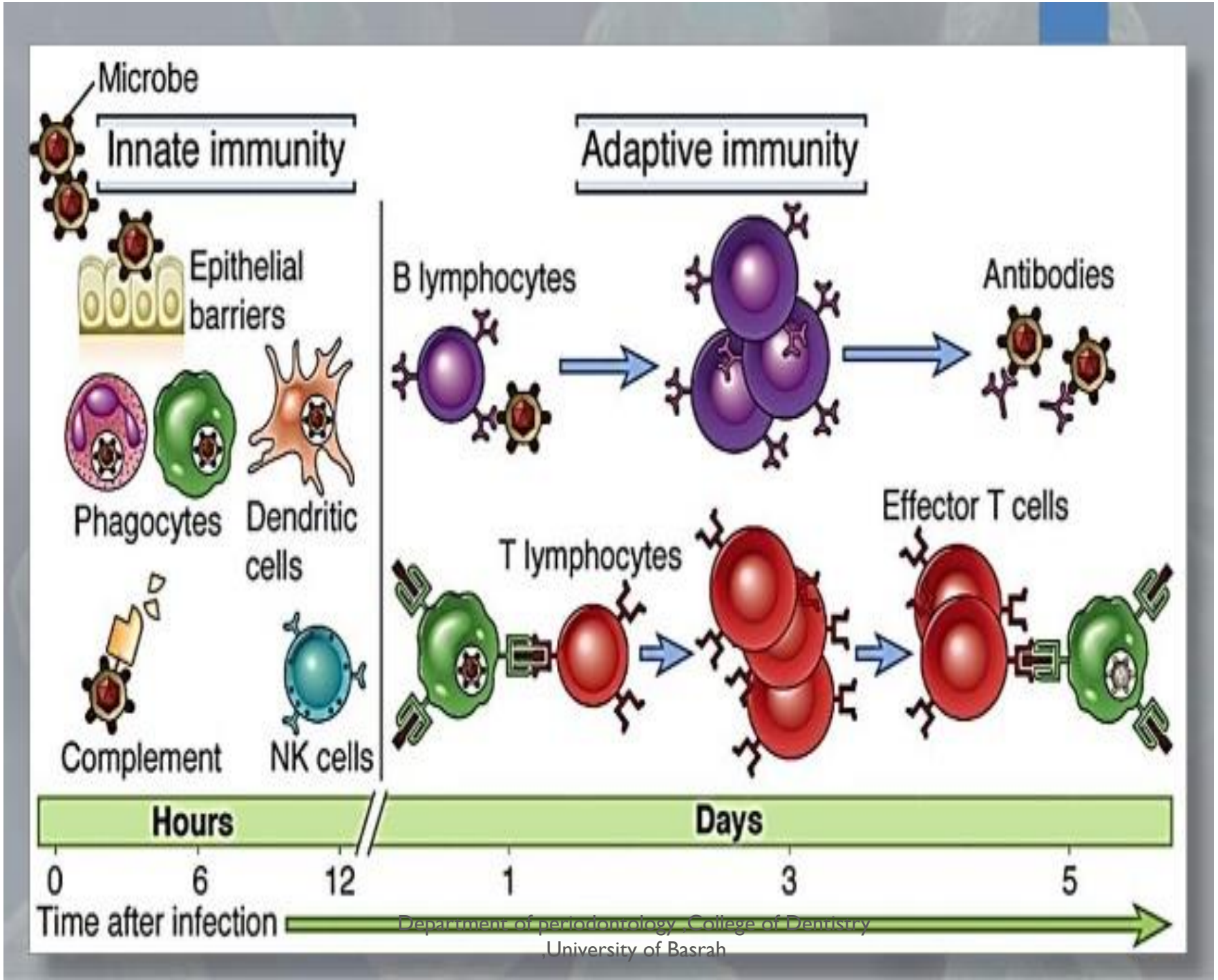
Refers to antigen-specific immune responses. Adaptive immunity has evolved to provide a focused and intense defense against infections that overwhelm innate immune responses.

- Adaptive immunity is second line of defence characterized by memory and specifity and divided into:

1)Humoral response.

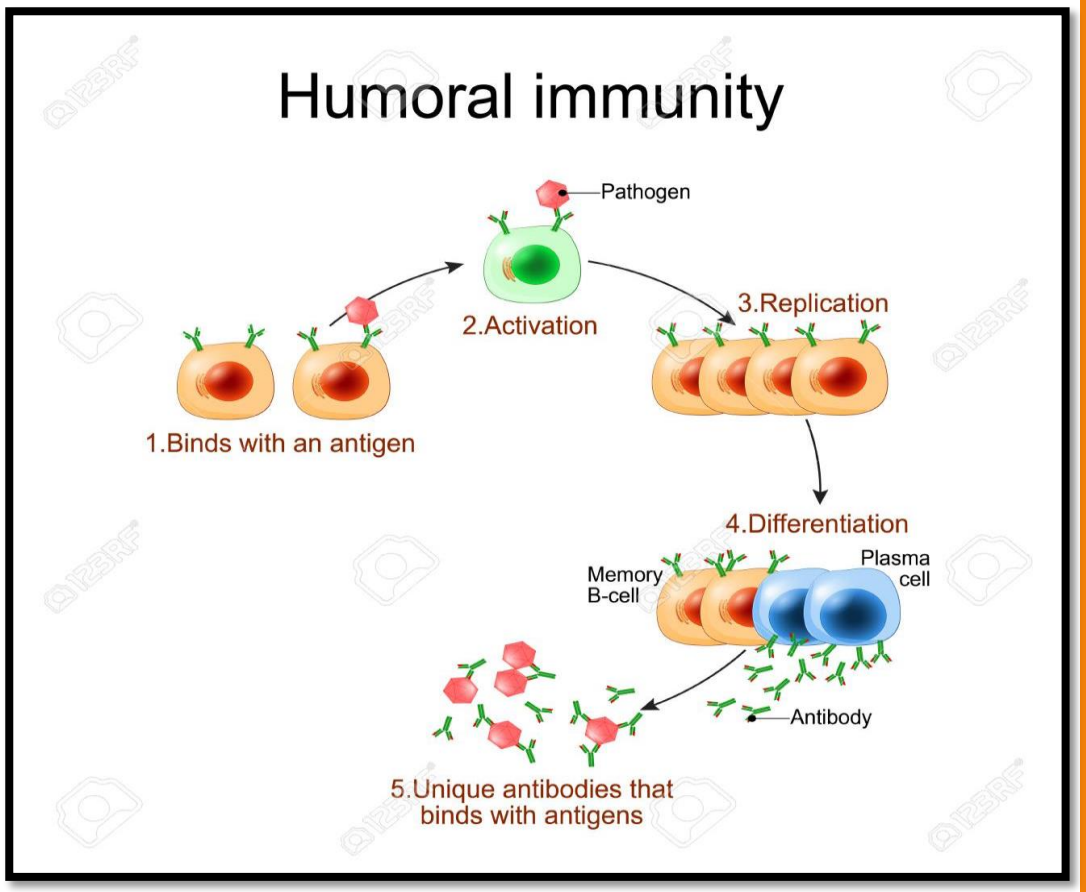
2)cell- mediated immunity.

- **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.**


Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
B lymphocytes
Antibodies
Phagocytes
Dendritic cells
T lymphocytes
Effector T cells
Complement
NK cells
Hours
Days
0
6
12
1
3
5
Time after infection

Humoral immunity

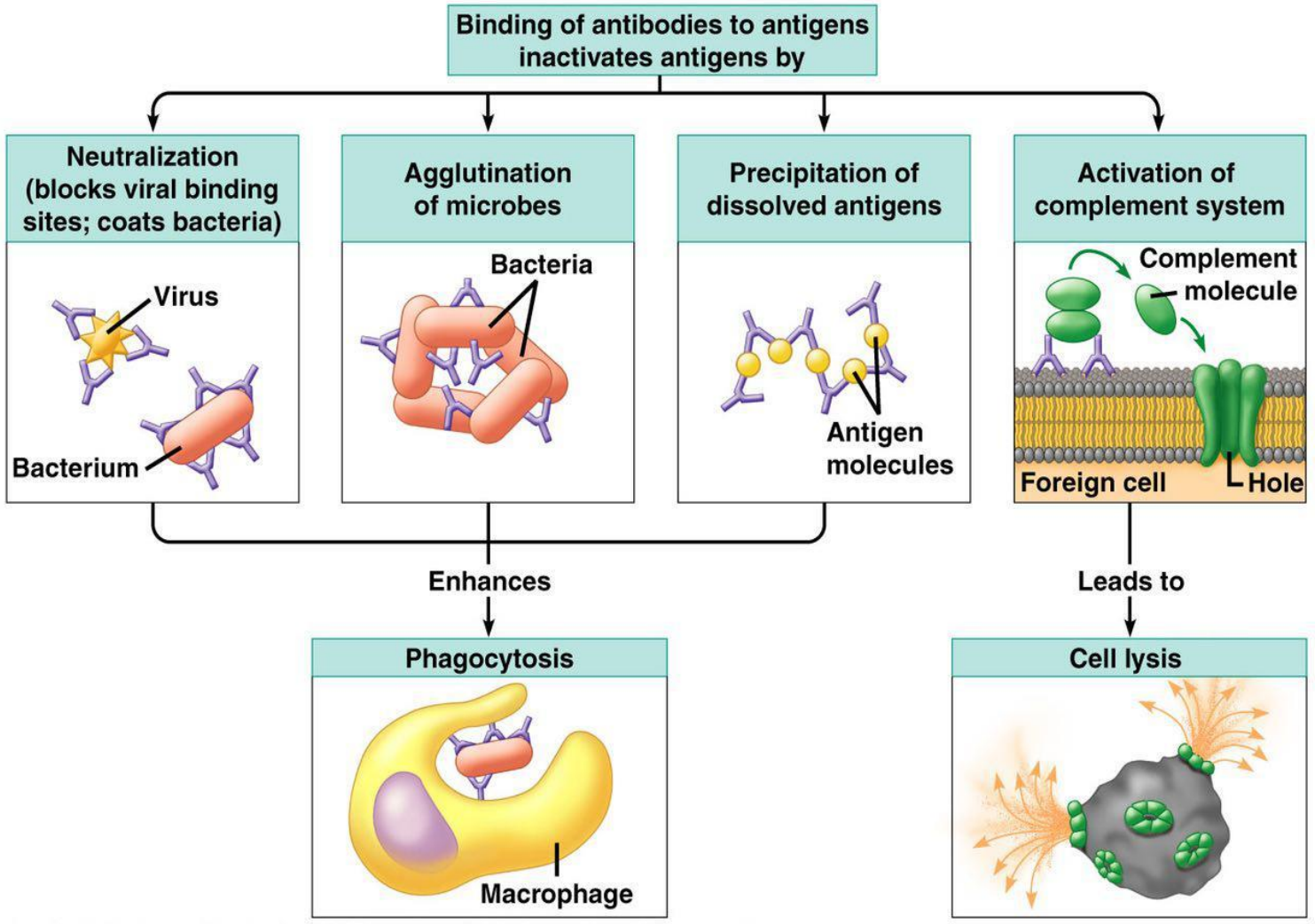
Specific antibodies (immunoglobulins), located in fluids such as plasma or gingival crevicular fluid , have the ability to bind to the antigen. This type of host defense is called **humoral immune response**. It is important to consider antibody function, i.e. the ability of an antibody to opsonize bacteria and to bind strongly to fimbriae and hereby prevent bacterial colonization .By the process of binding to the antigen, the antibody activates different effectors systems, e.g. complement . The activation of the complement system in turn mediates PMN and macrophage migration and phagocytosis. The process in which the antibody contributes to the elimination of antigens by enhancing phagocytosis is termed **opsonization**.



- Several studies suggest that assessments of the titer of a patient's antibody to various microorganisms in the subgingival biofilm may be useful in the differential diagnosis and classification of periodontal diseases. Antibodies of different subclasses have different properties.

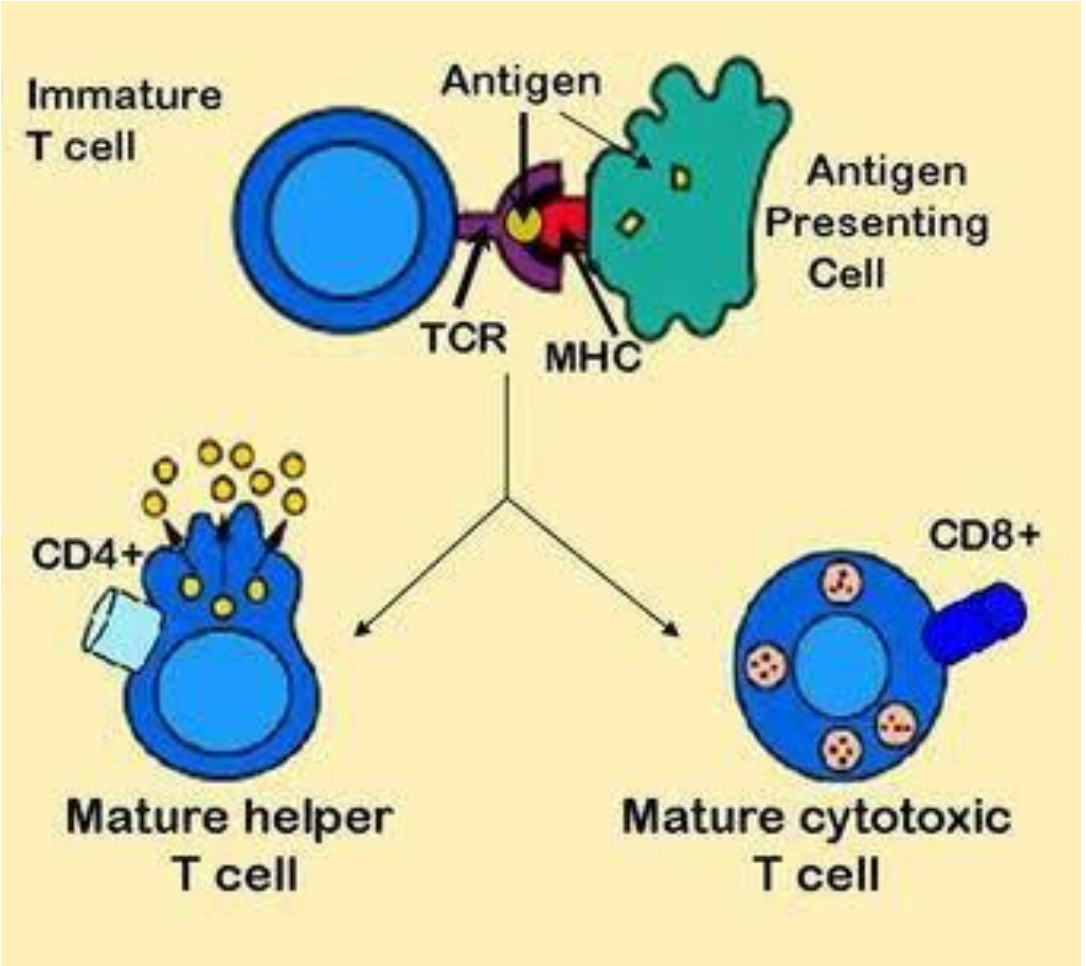
- Thus, IgG2 antibodies are effective against carbohydrate antigens (LPS) whereas the other subclasses are mainly directed against proteins. The proportions of plasma cells producing IgG and IgA subclasses were similar to the proportions of these immunoglobulin subclasses in serum. IgGI - producing plasma cells were predominant (mean 63%) in the gingival fluid ; followed by IgG2 - producing plasma cells (23%), while IgG3 and IgG4 - producing cells were present in much smaller numbers (3% and 10%, respectively).

Functions of Antibody



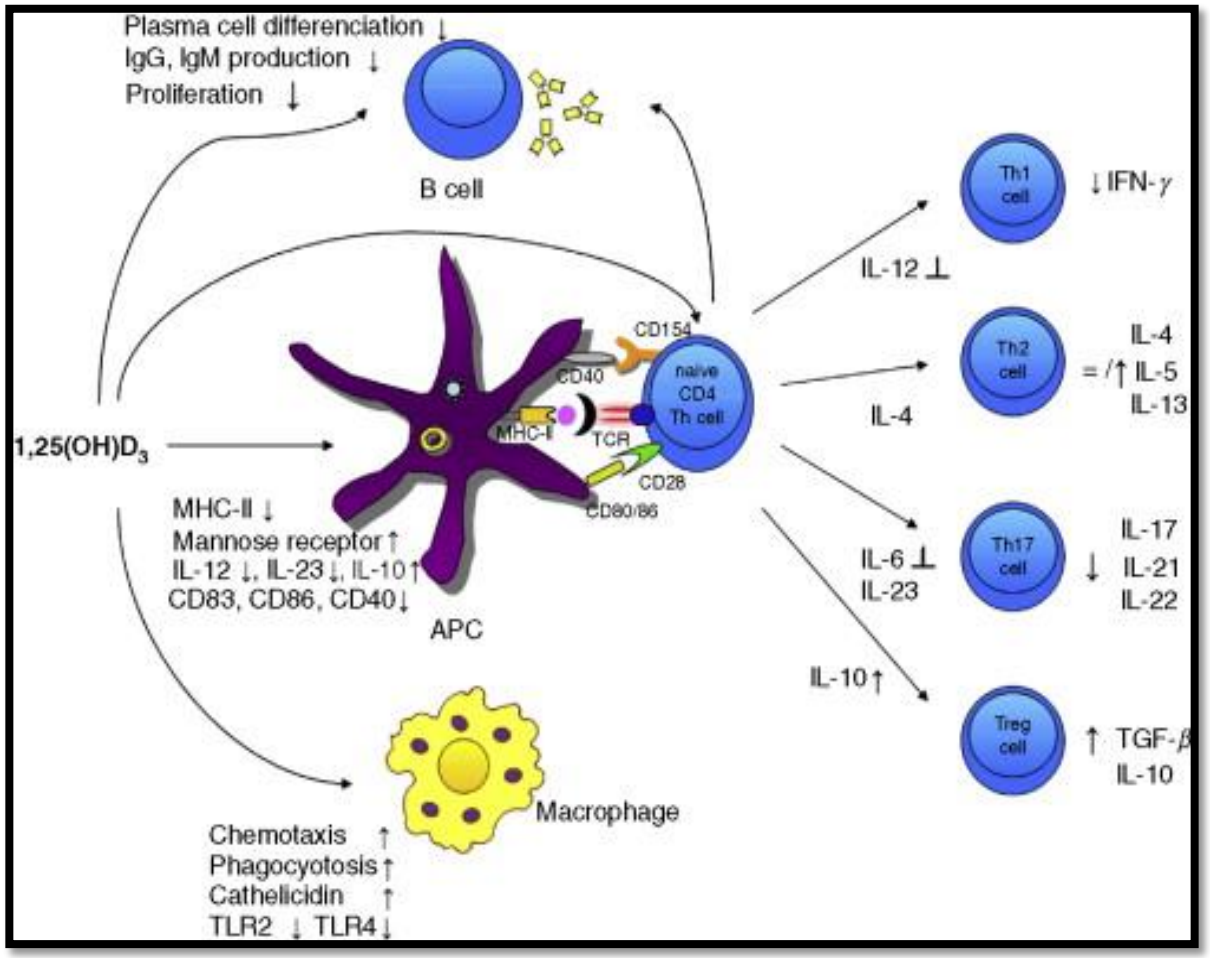
Cell- mediated immunity

Cell mediated immunity is an immune response that does not involve antibodies, but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.



Cells of the adaptive immune system , e.g. T and B lymphocytes have also been implicated as effectors in the pathogenesis of periodontitis. Macrophages and dendritic cells secrete cytokines that aid in migration and activation of these lymphocytes. Upon activation by antigen presenting cells, T lymphocytes proliferate and differentiate into subsets, including T helper (Th) cells, cytotoxic T cells and regulatory T cells (Treg).

Th cells can be further separated into Thl, which secrete interferon gamma (IFN-y), IL-2, IL-12, TNF-a and TNF-B leading to the eradication of intracellular pathogens;



- Th2 which secrete IL-4, IL-5, IL-6, IL-9 and IL-13 stimulating antibody production by B cells and contributing to the eradication of extracellular pathogens and T17 cells which are pro-inflammatory and pro-resorptive. Treg cells secrete IL-10 and TGF-B, which are anti-inflammatory cytokines.

- Alterations in the Th cell population subsets may lead to disease progression. For example, Th1 response has been reported to result in ' stable ' periodontitis and a Th2 response may result in disease progression , possibly due to the activation of B cells . B cells and their differentiated subtypes, plasma cells, which secrete antibodies, have been found to be the most prominent immune cell type within periodontal lesions.


Thank You
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DE LEON
and
CHRISTOPHER
JAMES REEVES