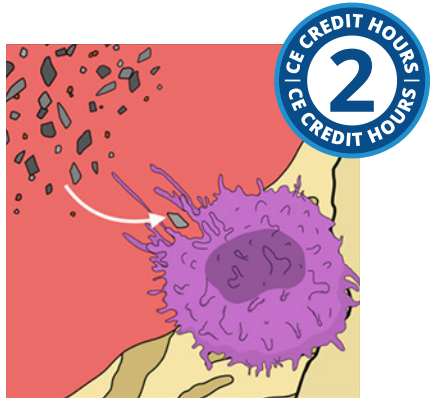


## Immunological and Inflammatory Aspects of Periodontal Disease



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### Conflict of Interest Disclosure Statement

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### Introduction – Hand Hygiene

This course reviews key components of the immune system and their coordinated roles in preventing and eliminating the etiologic agents of disease. Current concepts in the immunopathogenesis of periodontal and peri-implant diseases will be discussed with emphasis on the role of inflammation in tissue destruction.

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## Overview

The course reviews key elements of immunity and the role of the immune system in periodontal and peri-implant inflammation. The most current concepts in the progression of the periodontal lesion leading to alveolar bone loss will be discussed.

## Learning Objectives

**Upon completion of this course, the dental professional should be able to:**

- Define innate and adaptive or acquired immunity.
- Describe principal components of innate and acquired immunity.
- Compare and contrast the five classes of

immunoglobulins.

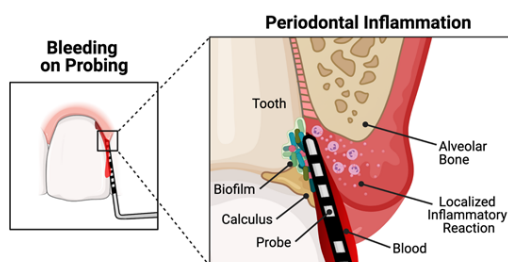
- Name the major types of leukocytes.
- Summarize the four types of hypersensitivity reactions to foreign substances.
- Discuss the origin, maturation, and function of T-cells and B-cells.
- Understand the role of bacterial complexes in periodontal disease.
- Discuss the role of inflammation in periodontal tissue destruction.
- Understand the etiology of inflammatory peri-implant disease.
- Recognize key distinctions between periodontitis and peri-implantitis.

## Homeostasis and Immune System

Periodontal disease pathogenesis is a fascinating subject. The oral soft tissue barrier is unique across all human body systems in that it surrounds mineralized (teeth) or metal (implants) transgingival fixtures that are necessary for mastication and speech. This unique environment requires very different immune vigilance as compared to other parts of the body to prevent bacterial invasion to the tissues and the bloodstream. The immune system in the mucosal soft tissue barrier is continually working to keep the internal environment in a condition of homeostasis.

In the oral cavity, the bacterial challenge is also very unique because the bacteria do not live in planktonic state but for the dental plaque, which is an organized biofilm community that consists of microorganisms that live in synergy to survive host defenses. This biofilm can either live symbiotically with the human host in which case it does not cause pathogenicity. This homeostatic state of biofilm-host immune interactions is clinically referred to as "Health". Thus, it becomes apparent that health is so much more than the mere absence of disease. Homeostasis is a dynamic state that cannot be defined merely as an absence of inflammatory disease signs. For instance, bleeding on probing (BOP), which is the key clinical sign of gingivitis (aka bleeding gums), is oftentimes a sign of effective immune surveillance and homeostasis. The prevalence of gingivitis is up to 80% in adult dentate patients. BOP is part of a homeostatic mechanism to effectively protect host integrity through elimination of bacteria.

The bacteria within the biofilm are capable of initiating the gingival lesion by triggering a localized inflammatory reaction. The host immune system responds to this bacterial challenge through an array of coordinated but complex processes that are designed to eliminate the initiating agent(s) and return the site to a state of homeostasis (Figure 1). However, if this inflammatory response is not successful in resolving the bacterial trigger and perpetuates into chronic persistent gingivitis, then the risk for progressing periodontal inflammation that may resorb the bone increases. The severity and extent of destruction of the periodontium is often related to a combination of factors such as the virulence of the biofilm bacteria, the robustness of the immune response and the chronicity of the inflammatory lesion that will be broached in this course.



**Figure 1.**

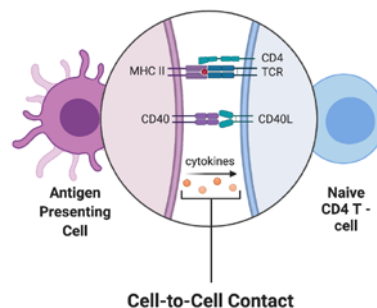
## Language of the Immune System

The immune system has elegantly evolved through centuries of human generations to a highly conserved set of cells that fulfill communications and execution roles through signaling molecules that are collectively referred to as mediators. The key players of the immune system remain the same across body sites and even across other species in the kingdom. What changes is the level of activation of different cell types in response to the environmental signals present within each unique system. For instance, due to the presence of teeth and the underlying supporting bone, the manifestation of inflammatory disease in the oral periodontal mucosa is fundamentally different to inflammation in the adjacent esophageal mucosa. Nonetheless, in both cases it is primarily driven by the same non-specific

response cells that collectively compose the innate immune system, which is a first line of response to pathogens and danger signals. Once the initial response is mounted, then specialized cells that belong to the adaptive system are signaled and become trained to the specific environmental trigger. The remainder of the chapter will delineate the key players that together form the immune system and discuss their roles in oral inflammation.

## Pathogen Recognition in Periodontal Soft Tissue Barrier

Much progress has been made over the last several decades in unraveling the complex nature of our immune system. The ability of our immune system to protect us is dependent upon the ability of immune cells to communicate with one another in order to coordinate activities. Cells are able to communicate with one another through cell-to-cell contact or by secreting small signaling proteins called cytokines. Cell-to-cell contact and/or reaction to cytokines is mediated through a diverse variety of membrane bound receptors and ligands that are expressed on the surface of the cell at the right moment. Ligands are molecules that bind to receptors initiating a signal. Literally hundreds of these receptors and ligands have been identified by immunologists all over the world. Today each receptor is referenced using an international language called the “Cluster of Differentiation” or CD. A number identifying the order in which the receptor was discovered follows the letters CD. For example, all T lymphocytes express the receptor CD3. However, a special type of T lymphocyte called a “Helper” T Cell, also expresses the receptor referred to as CD4.



**Figure 2.**

## Key Elements of Innate Immunity

Before examining the specifics of oral infections and the host response, several key elements involved in immunity will be summarized. In higher animals, resistance to a pathogen includes a non-adaptive, non-specific or innate response (natural immunity) and an adaptive or acquired response, which act in concert to protect the host. A simple way to remember this is to consider innate immunity as what you are born with. The innate response occurs in the same way and to the same extent regardless of how many times a pathogen is encountered. In contrast, an adaptive or acquired response occurs after a pathogen comes into contact with the host and a “specific response” to that pathogen is developed and stored in a memory bank for any future contact. On second contact with the pathogen, a more rapid and heightened immune response ensues to eliminate it.

### TLR4 and Bacterial Endotoxin

One of the best characterized systems of innate immune activation is the Toll-Like-Receptor (TLR) 4. TLR4 is a membrane receptor in phagocytes that is specialized to identify bacterial lipopolysaccharides (LPS). LPS is a key part of the cell membrane of Gram-negative bacteria, which has endotoxin properties. Endotoxins are generally associated with pathogenicity and are a key part of the virulence of known periodontal pathogens, such as the red complex bacteria *P. gingivalis*, *T. denticola*, *T. forsythia*. The key tissue resident surveilling cells of the innate immune system are called macrophages (Figure 3a). The name macrophages comes from the Greek “macro-” meaning “large” and “-phage” meaning “eater”. This is descriptive of the characteristics of the macrophage as a key phagocytic cell that can engulf large bacteria or particles up to its relative size of ~10µm. The critical activity that is necessary for the macrophage to eat the

invading pathogens and eliminate the danger is recognition. Recognition is critical for activation of both effector and signaling downstream responses. Specialized complexes called Pattern Recognition Receptors (PRRs) exist on the macrophage including the TLR4 membrane receptor. Each receptor is highly specialized to identify specific Pathogen-Associated Molecular Patterns (PAMPs), which in the case of TLR4 is LPS. In response when a macrophage’s TLR4 recognizes LPS, it initiates the phagocytic process and secretes inflammatory cytokines. One of the key functions of these cytokines is to rapidly recruit immune cells from the circulation which serve as a backup to clear the threat. For instance, IL-8 is a well-established chemokine signal that recruits neutrophils from the circulation. Through diapedesis, the process of transmigration of blood cells to the tissue that results in extravasation these neutrophils follow the IL-8 gradient to the site of inflammation and employ their phagocytic capacities and robust oxidative burst capabilities to contribute to pathogen clearance (Figure 3b). Monocytes are also recruited to the area and become differentiated to macrophages to further support the battle against invading pathogens. During this process the dilation of capillaries and extravasation of cells and fluid to the tissues results in the typical calor, rubor and tumor that clinically manifest as redness and swelling of the gingival tissues. If the host cells can effectively clear the microbial challenge leading to pathogen removal, the pro-inflammatory signaling ceases and an equilibrium is again established to support homeostasis (Figure 3c).

Innate immunity includes the following component parts:

- External barriers such as skin, oral mucosa, body secretions and even endogenous (normal) microbial inhabitants

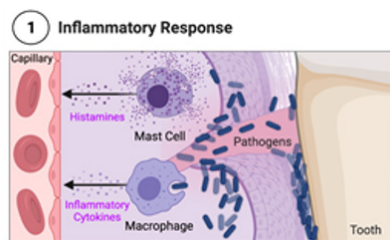


Figure 3a.

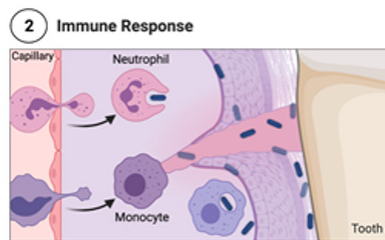


Figure 3b.

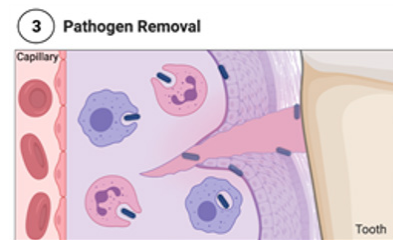


Figure 3c.

- 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

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

### Link of Innate to Adaptive Immunity: The IL-17/TH17 Axis

Mechanisms of innate and adaptive immunity work both separately and in concert within the oral cavity, where the oral mucosa serves as the primary barrier to a multitude of environmental and microbial challenges. In the periodontium, the sulcular and junctional epithelium represent an anatomic entry point highly susceptible to microbial translocation from dental biofilm. This barrier is only several cells thick and deteriorates in states of inflammation.

Neutrophil recruitment and homeostasis are essential to maintaining a functional state of innate immune surveillance. In sites of infection or inflammation, peripheral clearance of apoptotic neutrophils is performed by macrophages and dendritic cells, suppressing the release of proinflammatory cytokines interleukin (IL)-23 and IL-17. IL-17 is produced by conventional adaptive T helper 17 (TH17) cells and innate-acting lymphocyte populations, both of which are present in mucosal surfaces.

Physiologic mechanical stimulation, such as the low-level trauma incurred during mastication, influences gingival TH17 cells to aid in the recruitment of neutrophils and production of

antimicrobial peptides, thus serving to regulate tissue homeostasis in an IL-17 dependent manner. IL-17 plays a key role in periodontal immunity and has been shown to be required for immunologic defense against oral infections such as candidiasis. Alternatively, TH17 cells can influence osteoblasts to produce the osteoclastogenic cytokine, RANKL, and TH17 cells can even produce RANKL themselves. Excessive TH17 is associated with periodontitis, in which a dysbiotic microbiome triggers the pathogenic TH17/IL-17 response associated with periodontal tissue destruction and bone loss.

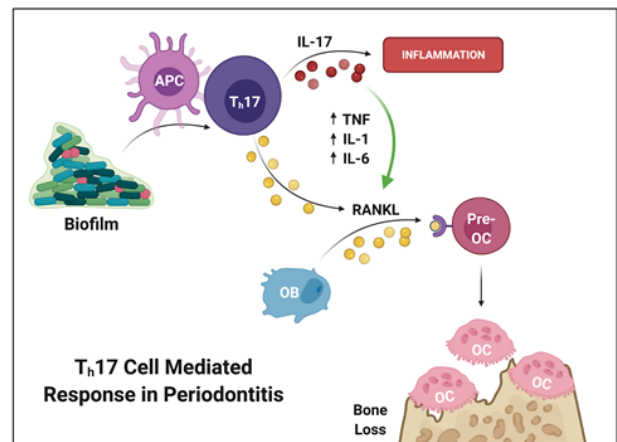


Figure 4.

### Three Important Characteristics to Adaptive Immunity

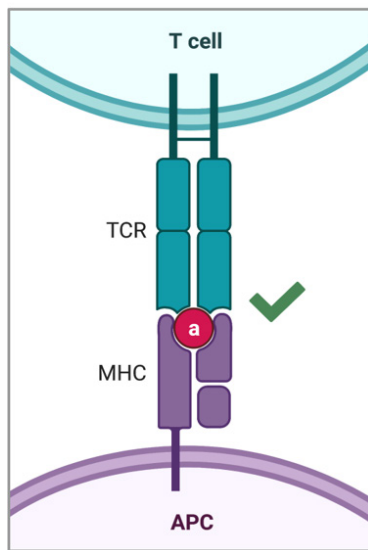
#### Self-Recognition

In healthy, immune competent individuals, immune responses are not produced against “self”-components. In vertebrates, Major Histocompatibility Complexes (MHC) exist that allow for differentiation between self and non-self antigens. In humans it is called the Human Leukocyte Antigen System (HLA) and it is responsible for genetically encoding our cells for recognition by the Immune System as either self or non-self.

Nucleated cells express MHC Class I genes, whereas a subgroup of immune cells called antigen presenting cells (APCs) express MHC Class II genes. In a healthy cell, a MHC Class I molecule coupled with one of the cell’s peptides is expressed at the cell surface. This complex



## Antigen Recognition



acts as a signal to circulating Natural Killer lymphocytes or cytotoxic T cells not to attack. However, if that cell is invaded by a pathogen, the MHC Class I molecule couples to a non-self peptide of the pathogen which then signals the cytotoxic lymphocytes to attack and destroy the cell. Tissue cells that undergo malignant transformation may also express peptides with the MHC Class I molecules that are no longer recognized as self, thus promoting the destruction of these cancerous cells.

## Specificity

This property refers to the ability of the immune system to recognize non-self antigens and respond in a specific manner to them, rather than responding in a random manner. Specificity is initiated by Antigen Presenting Cells such as activated T Cells, B Cells, macrophages, dendritic cells and thymic epithelial cells. The APCs express MHC Class II molecules at their surface, which are coupled to antigenic peptides. When this antigenic peptide is presented to a T cell, the T cell becomes activated and in turn helps stimulate B cells to proliferate and differentiate into Plasma Cells which make antibodies "specific" to that antigen only. When the body encounters the measles virus, for example, and responds to it, it does not respond against all other viruses.

## Memory

The initial contact with a molecule eliciting an immune response (antigen) leaves an imprint of information. With the help of the activated T cell, B cells also produce memory cells with antigen-specific antibodies expressed on their surface as B cell Receptors. These memory cells live for a longer period of time and, on second contact with an antigen, can respond more robustly and more quickly to eliminate it. We rarely suffer twice from measles, mumps, etc. The first contact imprints "memory" so that the body repels the next invasion.

Vaccines are synthetic forms or processed natural antigens used to stimulate the production of antibodies. Every time that antigen invades the body, the body remembers (memory), and an appropriate and specific response is produced by the host immune cells and antibodies.

## Immunogens and Antigens

Foreign material, including microorganisms, can contain chemical groups recognizable by the body as foreign. In general terms, molecules of any chemical group that elicit an immune response are termed immunogens. More specifically, a molecule that is capable of **generating** an **antibody** is termed an **antigen**. Antigenicity is determined by areas on the molecule termed antigenic determinants or epitopes. If a microorganism bypasses the body's other defenses, the immune system will produce a specific response that is directed against a particular antigenic epitope of this microorganism.

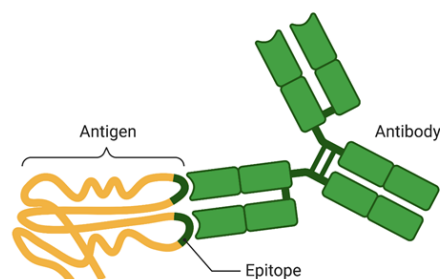


Figure 6.

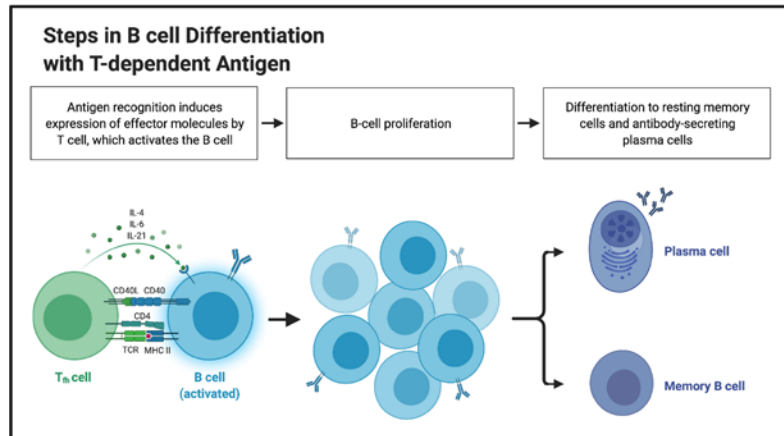


Figure 7.

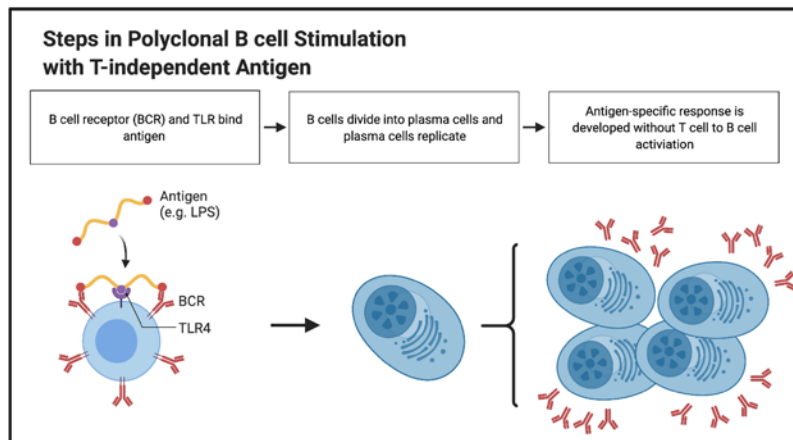


Figure 8.

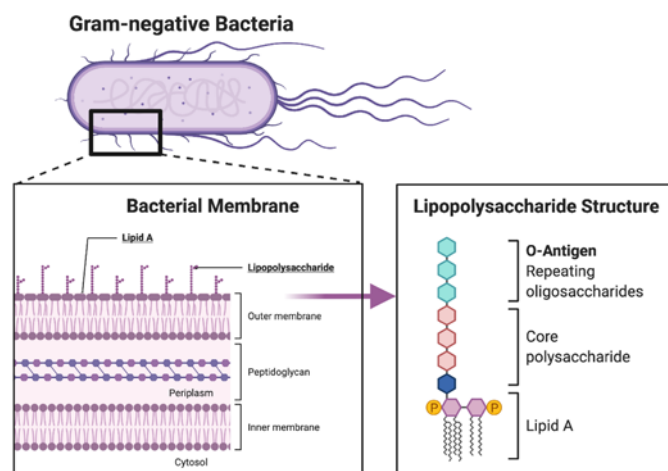


Figure 9.

Most antigens are pure proteins, glycoproteins or lipoproteins. T Cells recognize the small peptides of proteins but not polysaccharides or nucleic acids. An Antigen Presenting Cell (APC) can present one of these antigenic peptides to the T Cell, thereby activating it. The activated T cell will in turn join to a B Cell stimulating it to differentiate into a Plasma Cell, which will produce specific antibodies to that particular antigen. This type of antigen that requires a T Cell to B Cell interaction for antibody production to occur is referred to as a T-dependent antigen.

On the other hand, B Cells can express antibodies on their surface membrane, which are called B Cell Receptors (BCR). These receptors recognize not only proteins, but also polysaccharides and nucleic acids. These latter molecules are large and contain several different antigenic epitopes each of which can cross-link the membrane bound cell receptors (antibodies) on different clones of B Cells stimulating each cell to produce an antibody to one of the epitopes. This pathway is referred to Polyclonal B Cell stimulation.

Since these antigens do not require a T Cell to B Cell interaction in order to produce antibodies, they are referred to as T-independent antigens. Examples include bacterial polysaccharides such as Lipopolysaccharide (LPS), a virulent product of many gram-negative bacteria.

### Immunoglobulins

Immunoglobulins (Ig) are gamma globulin proteins present in bodily fluids (e.g. blood serum) and mucosal secretions (e.g., saliva, tears, vaginal secretions), and may also be found at the site of inflammation within the tissue. They are produced by plasma cells, which are differentiated B lymphocytes or B cells. Based on structure and protein composition, immunoglobulins are divided into five classes, two of which are further sub classified. Each has its own distinct chemical structure and specific biological function.


### Typical Immunoglobulin Structure

The immunoglobulin molecule is composed of a Constant region and Variable regions.

The *Constant* region generally is unique to the Ig Class or Ig Subclass and confers its biologic activity. The *Variable* regions form a complex, conformational molecular arrangement for the attachment of each specific antigen.

### Five Classes [subclasses] of Immunoglobulins

- Immunoglobulin G (IgG) [subclass IgG1, IgG2, IgG3, IgG4]
- Immunoglobulin A (IgA) [subclass IgA1, IgA2]
- Immunoglobulin M (IgM)
- Immunoglobulin D (IgD)
- Immunoglobulin E (IgE)



Functional activity	IgG	IgA	IgM	IgE	IgD
Heavy Chain Symbol	$\gamma$	$\alpha$	$\mu$	$\epsilon$	$\delta$
Percentage in Serum	75%	15%	10%	0.004%	0.2%
Opsonization	Yes	No	No	No	No
Complement System Activation	Yes	No	Yes	No	No
Transplacental Passage	Yes	No	No	No	No

Figure 10.

### The five classes [subclasses] of immunoglobulins include:

- **IgG** - Immunoglobulin G is the main immunoglobulin present in the blood and represents 70% to 75% of the total immunoglobulin pool. Several forms (subclasses) of IgG cross the placental barrier and are responsible for defense against infection in the first few months of a baby's life.
- **IgA** - Immunoglobulin A provides localized antibody protection on mucosal surfaces. It is found in mucosal secretions such as saliva, tears, sweat, nasal fluids, fluids of the lung and colostrum, genito-urinary tract, and gastro-intestinal tract. It is a primary defense against microorganisms attacking



exposed mucosal surfaces. IgA functions by preventing the microorganism from adhering to, and penetrating, the mucosal epithelial lining.

- **IgM** - Immunoglobulin M is the major immunoglobulin present on the surface of immature B cells and is effective against microbes by binding with complement and causing agglutination and bacteriolysis. It is the first immunoglobulin to take part in the immune response and plays an important role in controlling bacteria that find their way into the blood stream (bacteremia).
- **IgD** - Immunoglobulin D is a trace antibody in the serum and is present on the surface of B cells. It may be involved in stimulating and suppressing these antibody producing cells in the manufacture of antibodies
- **IgE** - Immunoglobulin E is found in very low concentration in human serum, but it increases during allergic reactions and some parasitic infections. IgE is bound to high affinity membrane receptors (FcεRI) on mast cells in the tissue and basophils in the blood. Cross-linking of cell bound IgE by an allergen

elicits the release of inflammatory mediators like histamine and several cytokines. IgE is also the main immunoglobulin responding to infection caused by certain parasites.

Before we examine how these immunoglobulins function during inflammation and periodontal destruction, let's review the key cellular elements of the immune system, most of which are blood components. When an organism invades the body, the body's initial response is carried out by white blood cells.

## Blood Leukocytes

White blood cells, or leukocytes, can be classified into five major categories based on morphological and functional characteristics. They may also be classified as granular or agranular based on the presence or lack of granules (small particles) within the cell cytoplasm. Leukocytes defend against invading microorganisms either by stimulating specific cellular or humoral (antibody production) immune responses, or by phagocytosis.

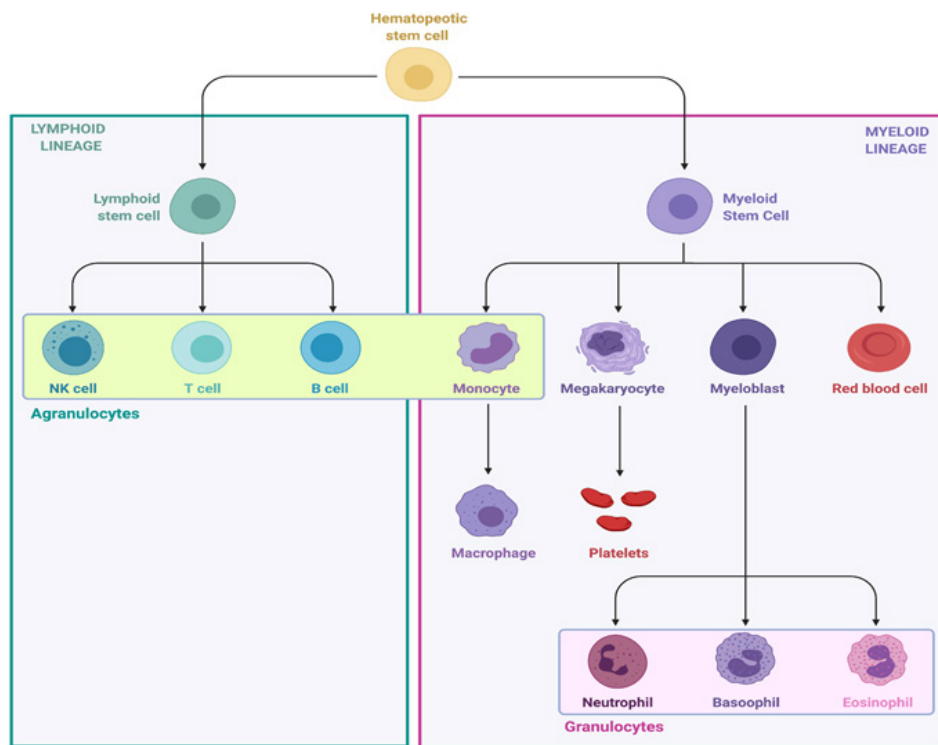


Figure 11.

**There are three types of granular leukocytes (granulocytes):**

- Neutrophils or polymorphonuclear leukocytes (PMNs)
- Eosinophils
- Basophils

Their names reflect the staining characteristics of the granules present in their cytoplasm. The name polymorphonuclear leukocyte also refers to the number of lobes comprising the nucleus of that cell type.

Monocytes, the fourth group of leukocytes, have few granules and a typically kidney-shaped nucleus. In tissue, monocytes become macrophages. Macrophages are capable of surviving months to years thereby providing important immune surveillance within the tissue of the various organ systems.

The last major group of leukocytes includes the lymphocytes. They are agranular round cells, with a proportionally large nucleus. Lymphocytes are primarily responsible for adaptive or acquired immunity.

**Granulocytes**

Neutrophils or PMNs are generally the first cells to migrate to the site of an invading microorganism or the site of trauma. This directed migration (chemotaxis) is caused by the release of signaling molecules called chemokines which can be released by several different cell types at the site of inflammation. The PMNs eliminate invaders by phagocytosis and other mechanisms. PMNs comprise 50-70% of the circulating leukocytes and more than 90% of the circulating granulocytes.

**PMN's have three types of granules:**

1. The primary or azurophilic granules are lysosomes that contain powerful digestive enzymes including acid hydrolases, elastase, myeloperoxidase and other proteins such as lysozyme and defensins.
2. Secondary or specific granules contain lactoferrin, lysozyme, collagenase and other proteins.
3. Tertiary granules contain gelatinase and other enzymes.

**Eosinophils** are involved in defense against parasitic infections and in control of allergic (hypersensitivity) reactions. Eosinophils comprise 1% to 3% of blood leukocytes.

**Circulating basophils** comprise less than 1% of leukocytes. Granules in basophils contain heparin, histamine, and serotonin. When these (and other) chemicals are released from the cell, they cause an acute inflammatory response, which is why they are collectively called mediators of inflammation. Basophils are related to mast cells, which are found in the tissues only. Mast cells and basophils are the cells involved in immediate hypersensitivity (Type I) reactions (anaphylaxis).

**Monocytes - Macrophages**

Monocytes, which constitute 3-7% of leukocytes, are usually the second cell type to move to the site of injury or inflammation. Monocytes, like PMNs, can eliminate pathogens and debris by phagocytosis. After leaving the circulation, monocytes develop into tissue macrophages.

Macrophages are active against infectious agents by phagocytosis. They are also important antigen presenting cells that take up antigen and, after processing, present the antigen to lymphocytes. Thus, macrophages can help orchestrate the immune response.

**Lymphocytes**

Lymphocytes comprise about 30% of the circulating leukocytes. Lymphocytes are involved in the development of adaptive or acquired immune responses. There are two major types of lymphocytes: T-cells and B-cells, both having surface receptors for antigen.

**The Antigen-Antibody Reaction**

When an antigen enters the body, two types of adaptive immune responses can occur:

- The synthesis and release of free antibody into the blood and other body fluids, called Humoral Immunity, is provided by B-cells.
- The production of sensitized lymphocytes called T-cells that are effectors of Cell-mediated Immunity.

**Cellular Immunity** involving T-cells is effective against fungi, many parasites, intracellular

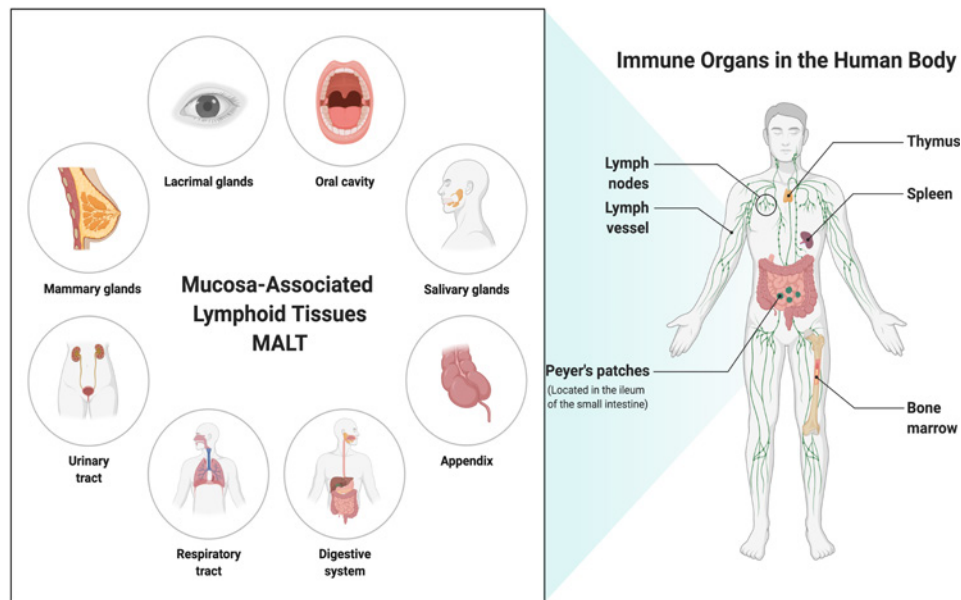


Figure 12.

bacteria, most viruses, cancer cells, and surgically transplanted or transfused foreign tissues. This is the type of response associated with graft rejection in transplant cases, and also with transfusion incompatibility.

**Humoral Immunity**, through circulating antibodies, is effective against extracellular organisms, including bacteria, some parasites, and some viruses.

Lymphocytes are produced in bone marrow from stem cells. A portion of the lymphocytic precursor cell population migrates to the thymus to mature into T-cells, while others are processed in the bone marrow to become B-cells. It should be mentioned that at 8-9 weeks of fetal development, B cells form in the liver but, soon after, the bone marrow becomes the primary site of production. The thymus gland and bone marrow are considered primary lymphoid organs while peripheral lymph nodes, mucous associated lymphoid tissue and the spleen are considered secondary lymphoid organs.

MALT is a significant component of mucosal immunity. It is the largest mammalian lymphoid organ system and comprises approximately 80% of all lymphocytes.

## Maturity of T and B Cells

### The T Cell:

T-cells mature in the thymus gland or in the lymph nodes. Since the thymus is only 10-15% functional in the adult, the lymph nodes take on greater importance in the maturation process.

**Thymus Gland:** T Cells migrating to the Thymus gland from the bone marrow will undergo a process of selection to eliminate not only the weakest cells, but also those so strong that they may attack healthy tissue cells (autoimmunity). Cells educated in the Thymus generally are either Helper (CD4+) or Suppressor/Cytotoxic (CD8+) cells. Other types of T-helper cells include T-helper 17, T regulatory cells, and T follicular helper cells.

**Lymph Node:** Naïve T cells in the paracortex of the lymph node may be activated by dendritic cells that have internalized and processed pathogenic antigens that made their way to the lymph node via lymphatic drainage from the site of infection or inflammation; or, by dendritic cells that have migrated to the lymph node from the site of infection. Once activated, T cells undergo clonal expansion and differentiate into functional effector cells (short-lived) or memory effector cells (long-lived). Functional effector cells migrate to the site of infection

or inflammation where they orchestrate T helper (CD4+) or T cytotoxic/suppressor (CD8+) functions to combat pathogens. Memory cells may enter the circulation or healthy tissue sites, or remain in the lymph node.

### The B Cell:

B cells mature in the bone marrow or in the lymph node.

**Bone Marrow:** Mature B cells express antibodies on their surface, which are specific for a particular antigen. The antibodies are expressed on the cell surface and are primarily IgM with some IgD. These cells circulate in the blood or home to sites of infection or inflammation. However, until they are activated by T-cells, they do not proliferate or differentiate to form antibody producing Plasma Cells. **Lymph Node:** Antigen-dependent B cells in the cortex of the lymph node may be stimulated by Helper T cells to proliferate and differentiate into Plasma Cells and memory cells. Immunoglobulin (antibody) class switching of the B cell from IgM to IgG, IgA or IgE may also take place as a result of the T cell interaction.

## Types of Hypersensitivity Reactions

The response of the host to the presence of foreign substances can trigger four types of hypersensitivity reactions:

### Type I: Immediate Hypersensitivity (Anaphylactic Reaction)

These allergic reactions are systemic or localized, as in allergic dermatitis (e.g., hives, wheal and erythema reactions). The reaction is the result of an antigen cross-linking with membrane-bound IgE antibody of a mast cell or basophil. Histamine, serotonin, bradykinin, and lipid mediators (e.g., platelet activating factor, prostaglandins, and leukotrienes) are released during the anaphylactic reaction. These released substances have the potential to cause tissue damage.

### Type II: Cytotoxic Reaction (Antibody-dependent)

In a cytotoxic reaction, the antibody reacts directly with the antigen that is bound to the cell membrane to induce cell lysis through complement activation. These antigens may be intrinsic or "self" as in autoimmune reactions or extrinsic or "non-self." Cytotoxic reactions

## Mast-cell Activation in Type I Hypersensitivity

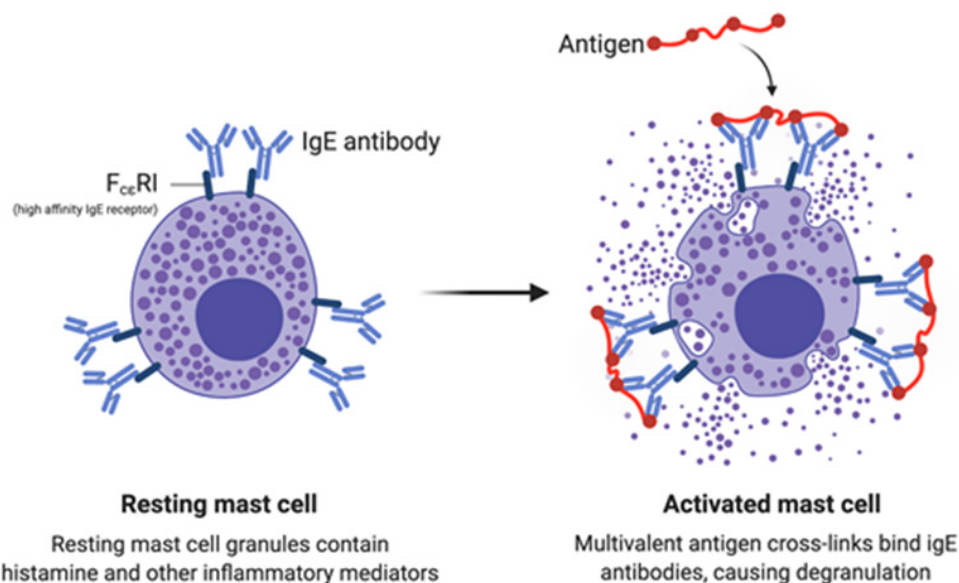


Figure 13.

## Types of Hypersensitivity Reactions

	Type I	Type II	Type III	Type IV		
<b>Immune Reactant</b>	IgE	IgG	IgG	T <sub>H</sub> 1	T <sub>H</sub> 2	CTL
<b>Antigen</b>	soluble antigen	cell / matrix associated antigen	soluble antigen	soluble antigen	soluble antigen	cell associated antigen
<b>Effector Mechanism</b>	mast-cell activation	phagocytes, NK cells (F <sub>c</sub> R+ cells)	FcR+ cells	macrophage activation	eosinophil activation	cytotoxicity
<b>Example of Reaction</b>	allergic rhinitis, asthma, systemic anaphylaxis	drug allergies i.e. penicillin	serum sickness, arthus reaction	contact dermatitis, tuberculin reaction	chronic asthma, chronic allergic rhinitis	contact dermatitis

Figure 14.

are mediated by IgG and IgM. Examples of cytotoxic reaction are the Rh incompatibility of a newborn, blood transfusion reactions, and autoimmune diseases like Pemphigus Vulgaris, Bullous Pemphigoid, autoimmune hemolytic anemia and Goodpasture's syndrome to name a few.

### Type III: Immune Complex Reaction

IgG and IgM bind antigen, forming antigen-antibody (immune) complexes. These activate complement, which results in PMN chemotaxis and activation. PMNs then release tissue damaging enzymes. Tissue damage present in autoimmune diseases (e.g., systemic lupus erythematosus), and chronic infectious diseases (e.g., leprosy) can be attributed, in part, to immune complex reactions.

### Type IV: Cell-Mediated (Delayed Hypersensitivity)

Cell-mediated reactions are initiated by T-lymphocytes and mediated by effector T-cells and macrophages. This response involves the interaction of antigens with the surface of lymphocytes. Sensitized lymphocytes can produce cytokines, which are biologically active substances that affect the functions of other cells. This type of reaction takes 48-72 hours, or longer, after contact with the antigen to fully develop. Many chronic infectious diseases,

including tuberculosis and fungal infections, exhibit delayed hypersensitivity. Evidence suggests that hypersensitivity reactions, particularly Type III and IV, may be involved in the pathogenesis of periodontal disease.

Evidence suggests that hypersensitivity reactions, particularly Type III and IV, may be involved in the pathogenesis of periodontal disease.

### Progression of the Inflammatory Periodontal Lesion

As with most infections, the inflammatory reaction within the gingival tissue serves to contain or stop a local microbial attack, and prevents the spread of attacking organism. However, a robust inflammatory reaction may also result in the destruction of surrounding cells, connective tissue matrix and eventually bone. The progression from relative health to advanced disease is best explained by reviewing the mechanisms of plaque induced inflammation and the immune components involved in initiating and propagating the inflammatory process.

Early visible inflammatory changes in the gingival margin occur within a few days if plaque growth is undisturbed. Within 10 to 20 days the plaque mass changes composition from



mostly gram-positive coccoid and filamentous bacteria to gram-negative rods and spirochetes. A gram-positive plaque is usually associated with periodontal health, while a gram-negative is associated with disease. This complex community of microorganisms is referred to as a biofilm.

Gram-negative and gram-positive microorganisms within the biofilm produce and release a variety of metabolic by-products that are toxic to host tissues. These include exotoxins, endotoxins, odor-producing metabolites (e.g., hydrogen sulfide) and many different tissue-degrading enzymes, including bacterial collagenase and various proteases.

Several of the more common periodontal pathogenic bacteria are grouped into complexes based on their association with the periodontal lesion. The most virulent of organisms form the Red Complex and consists of *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. The Orange complex is composed of *Prevotella intermedia*, *Prevotella nigrescens*, *Peptostreptococcus micros*, *Eubacterium nodatum*, *Streptococcus constellatus*, three *Campylobacter* species including *Campylobacter rectus*, and 4 species of *Fusobacterium*. These two complexes of periodontal pathogens become more prevalent in numbers and occurrence as the periodontal pocket deepens. *Aggregatibacter actinomycetemcomitans* serotype b, which is strongly associated with aggressive forms of periodontitis, appears to be an “outlier” (i.e., not placed into any grouping or complex, but very virulent just the same).

Other groups of periodontal biofilm bacteria that form the Blue, Yellow, Green and Purple Complexes primarily consist of tooth surface colonizers including *Streptococcus*, *Actinomyces* and *Capnocytophaga* species. The Red and Orange Complex bacteria, on the other hand, mostly colonize nearer to epithelial surfaces of the pocket wall. Certain strains (subtype of a microorganism) of the most virulent organisms, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Eikenella corrodens* have also been shown to invade epithelial

cells. This is a characteristic that allows the microorganism to evade the immune system.

Not all plaque-induced inflammatory lesions progress from gingivitis to periodontitis. A healthy immune response will protect the host by eliminating the noxious stimuli through coordinated response of the innate and acquired immune system. Lesions that do progress are the result of a heightened inflammatory response in a susceptible host. This response may be related to a variety of factors including: 1) the type and virulence of the bacteria in the plaque biofilm; 2) host immune defects that are genetically determined or acquired, such as in the Acquired Immune Deficiency Syndrome (AIDS); 3) decreased immune function resulting from medically related conditions (e.g., diabetes, leukemia and autoimmune diseases); 4) social habits such as drug and alcohol abuse and smoking; and 5) environmental factors such as stress and exposure to toxins.

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 which 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 cell membrane receptors called *Toll-like Receptors (TLRs)*. 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. There are 11 TLRs identified in humans of which TLR-2 and TLR-4 appear to be the most important.

When PAMPs (Table 1) bind to TLRs on the cell membrane, a molecular signal is produced which launches one of several different enzymatic pathways within the cell's

**Table 1. Pathogen Associated Molecular Patterns**

- Lipopolysaccharide (LPS): g (-) cell wall
- Peptidoglycan: g (+) cell wall, some g (-) cell walls
- Lipoteichoic acids: g (+) cell wall
- Mannose: microbial CHO -
- Flagellin: bacterial flagella
- Pilin: bacterial pili
- Bacterial nucleic acids
- Viral RNA
- Yeast cell walls: lipoteichoic acids, glycolipids, zymosan

cytoplasm. One of these pathways eventually will eventually signal the nucleus of the cell to begin production of certain types of molecules called cytokines. The result is an inflammatory response that is initiated by the release of these pro-inflammatory cytokines, and other soluble mediators of inflammation from the cell. The major pro-inflammatory cytokine is Interleukin-1 (IL-1 $\alpha$ , IL-1 $\beta$ , IL-1Ra), which is released by several different cell types including sulcular and junctional epithelium, fibroblasts, macrophages and PMNs. Some functions of IL-1 are listed in Table 2.

The release of IL-1 initiates a series of events that are usually associated with an acute inflammatory phase. Most of the events described below occur in an orchestrated manner to eliminate the pathogens.

- 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 not only release enzymes that are capable of destroying pathogens but also attach to antigen-antibody complexes for phagocytosis. PMNs will also migrate between junctional epithelial cells to reach the sulcus, where they literally burst and release their enzymes.
- Histamine and kinins released from tissue Mast cells promote vasodilation and increase vascular permeability, enhancing the influx

**Table 2. Functions of Interleukin-1**

- Up-regulates complement and Fc receptors on neutrophils and monocytes
- Up-regulates adhesion molecules on fibroblasts and leukocytes
- Up-regulates adhesion molecules on endothelial cells
- Induces homing receptors for lymphoid cells in the extracellular matrix
- Induces osteoclast formation and bone resorption (RANKL)
- Stimulates MMP and prostaglandin production by macrophages, PMNs and fibroblasts
- Up-regulates MHC expression by B and T cells for activation, clonal expansion and immunoglobulin production
- Induces interleukins 2, 3, 4, 5, 6, 7, 8, 10, 12, & TNF- $\alpha$

of cells and protein molecules such as antibodies and complement.

- Plasma proteins called Complement will be activated through a cascade of enzymatic reactions. There are three pathways for the activation of complement: The Classical (Figure below); Alternative; and Mannose-binding lectin.

Complement has several biologic functions

- C3a activates basophils and mast cells causing release of vasoactive substances including histamine.
- In concert with antibodies, C3b and C4b opsonize, or clump, the antigens together for easier phagocytosis by PMNs and macrophages
- C5a and C5a des Arginine enhance PMN activation and chemotaxis
- C5b, C6, C7, C8 form a Membrane Attack Complex (MAC) that can destroy bacteria by punching holes in their cell wall.

The antibodies entering the tissue come from the circulation. Some may be specific for certain pathogen-associated antigens and come from the IgG and IgA classes and subclasses. Others that are less specific or of weaker affinity will be of the IgM class.

PMNs and gingival fibroblasts may release enzymes called matrix metalloproteinases, or MMPs (Table 3). These include collagenase and elastase that are capable of breaking down extracellular matrix like collagen fibers.

**Table 3. Matrix Metalloproteinase (MMP)**

- MMP (Zn++) enzymes digest extracellular matrix
- MMP-1, 8, 13: Collagenases (FØ, PMN)
- MMP-2, 9: Gellatinases
- MMP-3, 10, 11: Stromylysins
- MMP-7: Matrilysins
- Membrane anchored MMPs: 14, 15, 16, 17, 24, 25

In addition, several cell types will be induced by Il-1 to produce Prostaglandin (PG), a by-product of the enzymatic breakdown of arachidonic acid found in the lipid layer of a cell membrane. All nucleated cells except lymphocytes produce PG. 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.

*Clinically*, the manifestation of these events results in the early stages of gingivitis. There may be bleeding on probing, slight gingival swelling along with mild erythema (reddening) of the tissue, and increased flow of gingival crevicular fluid. *Microscopically*, the inflammatory infiltrate is predominated by PMNs located primarily around vessels within the connective tissue, just below the junctional epithelium (JE). Loss of some perivascular collagen will also be seen. Within the lamina propria (connective tissue layer beneath epithelium) of the sulcular epithelium, the number of dendritic cells called Langerhan's cells will increase. These cells can internalize and process pathogen-associated antigens and migrate, via lymphatic channels, to the lymph node where they become Antigen Presenting Cells (APCs) to naïve (immature) T Cells. Free antigen may also travel to the lymph node, where macrophages or specialized

dendritic cells internalize, process and present the antigen to T Cells. Newly activated T Cells will in turn stimulate B Cells to switch immunoglobulin from IgM to IgG, IgA or IgE. The B Cell may also be stimulated to proliferate and differentiate into Plasma Cells which then produce the antigen specific antibody presented to it earlier by the T Cell.

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. The lipoxins (A and B) may act to 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. Thus, the inflammation resolves and tissue repairs. Other molecular compounds, called *Resolvins* and *Protectins*, are produced from the metabolism of dietary Omega 3, and act in a similar fashion to the lipoxins.

#### **Early Lesion (4-7 days)**

If the pathogens have not been eliminated, the immune response will intensify. Hallmarks of the Initial Lesion will continue, but will be accentuated. Clinically, there may be more swelling (edema) along with increased redness (erythema). Microscopically, the area of inflammatory infiltrate will increase, occupying as much as 10-15% of the gingival connective tissue beneath the junctional and sulcular epithelium. Loss of extracellular collagen may be as great as 60-70%, with cytopathic changes seen in the gingival fibroblasts. In an attempt to wall-off the growing lesion, JE cells will begin to proliferate in numbers.

Although PMNs are still prominent in number, lymphoid cells can now be seen accumulating subjacent to the junctional epithelium. Many of the lymphocytes come directly from the circulating blood responding to specialized chemokines that signal them to home to the site of the lesion. Other lymphocytes will begin to arrive from surrounding lymphoid tissue. 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. This is accomplished through the production of various cytokines, or by cell-to-cell interaction. 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, and enhance PMN and macrophage phagocytosis. This is probably why T Cells are linked to the “stable lesion” as in gingivitis, since they tend to keep the infection under control.

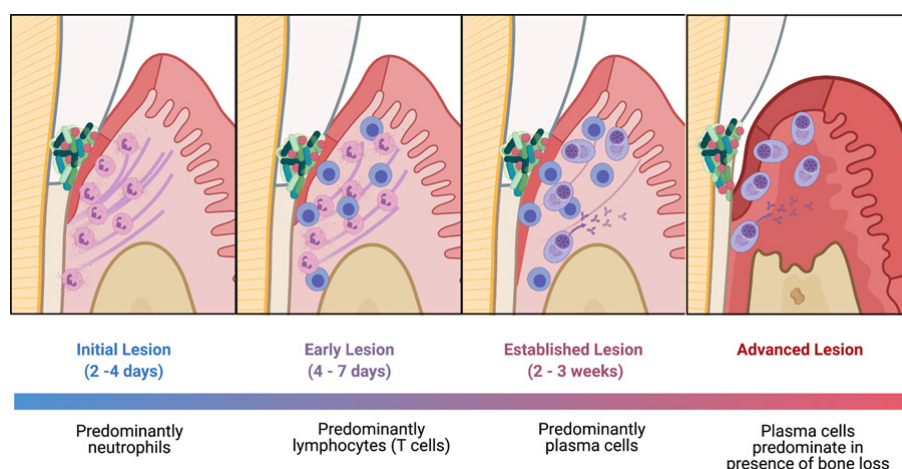
### Established Lesion (2-3 weeks)

If the T Cell is unable to effectively deal with the infection and it becomes chronic, a more robust immune response may be required. There is, however, a persistence of the manifestations of acute inflammation. The inflammatory infiltrate in the *Established Lesion* occupies a greater area within the connective tissue, with more destruction of collagen matrix. Again, the junctional epithelium will attempt to occupy the space and wall-off the infection by migrating laterally and apically, resulting in early pocket formation. 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), with receptors for the same specific antigen, will link to the B Cell and activate it. 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. Cytokines IL-3, IL-4, IL-5, IL-6, IL-10 and granulocyte-monocyte colony stimulating factors (GM-CSF), released by the T Cell, are important signaling molecules for proliferation and differentiation of B Cells.
- Other B Cells that express IgM antigen receptors may be activated independently of T Cell help. These B Cells respond to T-independent antigens, many of which are large bacterial carbohydrates that cross-link the IgM antibodies. In a similar manner, macrophages may also present multiples of the same antigen to B Cells for cross-linking of IgM.

### Advanced Lesion

Several of the features described for the *Established Lesion* will persist at this stage. Plasma Cells continue to be the predominant cell type within the inflammatory infiltrate.



**Figure 15.**

Further destruction of collagen subjacent to the junctional epithelium is seen, with fibrosis at distant sites. A prime characteristic of the *Advanced Lesion* is the extension of the lesion into the periodontal ligament and supporting bone. The resulting outcome is bone loss that is exhibited as clinical attachment loss and pocket formation. The mediators of inflammation that have been identified as playing a significant role in alveolar bone resorption include interleukin-1 $\beta$ , interleukin-6, Tumor Necrosis Factor- $\alpha$  (TNF $\alpha$ ), 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.

### Progression from Gingivitis to Periodontitis

While biofilm is the clear etiological agent of gingivitis, progression to a chronic periodontal lesion is largely determined by the host response to microbial dysbiosis. Disproportionate or uncontrolled immunologic and inflammatory responses lead to the tissue destruction characteristic of periodontal disease. Recent research has identified both pro-inflammatory and pro-resolving compounds that serve as critical mediators of inflammation. Pro-inflammatory mediators include cytokines, chemokines, and metalloproteinases, which are significantly elevated in periodontitis. Pro-resolving mediators are endogenous lipid compounds that serve to resolve inflammation, promoting monocytic resolution of inflammation and clearance of apoptotic neutrophils by macrophages, as well as anti-microbial defense mechanisms. Pro-resolving lipid mediators primarily consist of resolvins derived from either omega-3 fatty acids or lipoxins from arachidonic acid. Interestingly, arachidonic acid also gives rise to the pro-inflammatory compounds, prostaglandins and leukotrienes. It was thought for many years that inflammation resolution was the result of a passive decay of proinflammatory signals, however, it now appears pro-resolving mediators are important to arrest disease progression and actively reverse periodontal inflammation.

### Osteoimmunology

"Osteoimmunology" is a continuously evolving

area of scientific investigation. The term *osteo-immunology* specifically refers to the cross-regulation between bone cells and the immune system. One of the most important immune-related molecules involved in bone homeostasis is the Receptor Activator of Nuclear Factor  $\kappa$ B Ligand (RANKL). RANKL has been described as the "master switch regulator" of osteoclastogenesis. Since bone homeostasis is a balance between bone formation (osteoblastogenesis) and bone resorption (osteoclastogenesis), understanding the regulatory mechanisms between these phases may provide greater insight into bone diseases where the scale is tipped in favor of resorption. Since periodontitis is an inflammatory disease characterized by alveolar bone loss, controlling the expression of RANKL in the periodontal lesion may be a useful treatment approach.

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. This ratio appears to be more important in identifying bone resorbing sites than the concentration of either RANKL or osteoprotegerin alone. What is known about RANKL and the periodontal lesion?

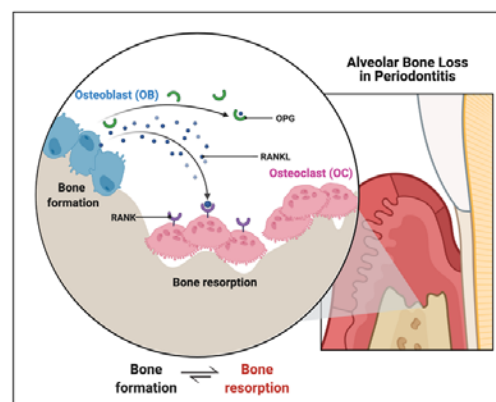


Figure 16.



- Gingival fibroblasts produce osteoprotegerin, which may help prevent bone resorption in the earlier stages of periodontal disease where the lesion is primarily confined to an area beneath the epithelium
- Osteoblasts and periodontal ligament fibroblasts express RANKL on their cell membrane. T Cells not only express membrane bound RANKL, but also secrete it in soluble form. The pro-inflammatory cytokines interleukin-1 $\beta$  and interleukin-6, interleukin-11, interleukin-17, Tumor Necrosis Factor- $\alpha$  and the eicosanoid Prostaglandin E2 signal these cells to express membrane-bound RANKL, and the T Cell to secrete RANKL. Recall that these molecules have already been shown to be increased in the periodontal lesion and indirectly involved in periodontal bone loss. Thus, when the lesion has advanced toward the periodontal ligament and alveolar bone, the up-regulation of RANKL may lead to bone loss and subsequent deepening of the periodontal pocket. In such a scenario, it appears that the T Cell plays a significant role in bone resorption.

The concentrations of osteoprotegerin and RANKL are controlled not only by the cytokines listed above but also by osteotropic hormones such as glucocorticoids and parathyroid hormone which inhibit osteoprotegerin and increase RANKL production. Estrogen appears to inhibit RANKL and RANKL-stimulated osteoclastogenesis.

### Peri-implantitis

Immune responses in the peri-implant soft tissue barrier are independently worthy of

mention because they are distinctly different to these around teeth. One of the most major advancements in our understanding of bone remodeling and inflammatory peri-implantitis around dental implants comes from the findings that titanium material breakdown can cause immune activation in the peri-implant tissues. It was recently shown that while titanium implants are extremely resistant to corrosion in atmospheric conditions, if these surfaces are abraded such as during dental hygiene procedures with metal instruments, the environment in the peri-implant crevice with the pH fluctuations, bacterial reducing activity and tribocorrosion all contribute to the release of titanium particles (Figure 17a). These titanium particles are in the submicron and micron range and activate macrophages and multiple other phagocytic and non-phagocytic cells to elicit pro-inflammatory responses. Thus by acting as an environmental threat these particles alter the local microenvironment both with direct effects, such as IL-1 $\beta$  and RANKL upregulation as well as indirect effects through the change of the local conditions that affect microbiome composition (Figure 17b). As a result immune surveillance in the peri-implant soft tissue barrier is modified by the presence of titanium and results in a different clinical response, which is consistent with the much more rampant tissue destruction in peri-implantitis as compared to periodontitis as well as the resistance to antibiotic and scaling treatments. This new data have paved the way for immunomodulatory treatments for peri-implantitis that may be impactful in its management.

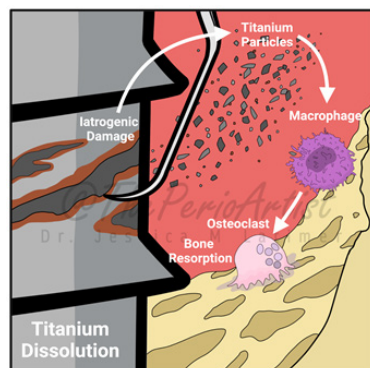


Figure 17a.

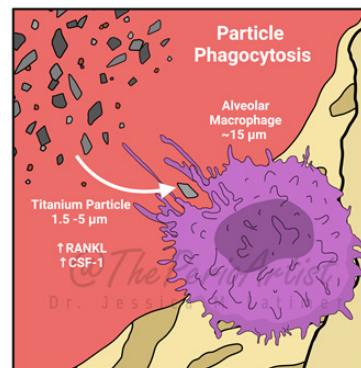


Figure 17b.

## Conclusion

The immune system is a complex array of cells and molecules operating in an orchestrated manner in order to protect the host from pathogenic microorganisms and exogenous noxious agents within our environment. However, destruction of host tissue may occur if the immune response is inadequate due to intrinsic or extrinsic mechanisms in cell function, or if there is a hyper-responsiveness due to dysfunctional regulatory mechanisms. The pathogenesis of periodontal disease is clearly of an inflammatory origin and, as such, has a close association with the Immune System. Unraveling the intricate mechanism by which the host responds to pathogens colonizing the tooth will lead to more sensitive means to detect subtle changes in disease activity, and more effective and predictable therapeutic modalities. The Figure below is a simplified model reminding us of the complex nature of periodontal disease.

## Course Test Preview

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1. **Protective mechanisms such as external barriers and bodily secretions are components of \_\_\_\_\_ immunity.**
  - A. innate
  - B. adaptive
2. **The key cells involved in developing adaptive or acquired immunity are \_\_\_\_\_.**
  - A. neutrophils
  - B. macrophages
  - C. T & B lymphocytes
3. **The immunologic principle involved with the ability of a vaccine to prevent disease is \_\_\_\_\_.**
  - A. self-recognition
  - B. memory
  - C. specificity
4. **The immunoglobulin responsible for defense against infection during the first few weeks of life is \_\_\_\_\_.**
  - A. IgG
  - B. IgA
  - C. IgM
  - D. IgD
  - E. IgE
5. **The first immunoglobulin to respond to an infection is \_\_\_\_\_.**
  - A. IgA
  - B. IgM
  - C. IgD
  - D. IgE
6. **The immunoglobulin involved in allergic reactions is \_\_\_\_\_.**
  - A. IgG
  - B. IgA
  - C. IgM
  - D. IgD
  - E. IgE
7. **The migration of neutrophils, or polymorphonuclear leukocytes (PMNs), to the site of an invading microbe is referred to as \_\_\_\_\_.**
  - A. gradient migration
  - B. diapedesis
  - C. chemokinesis
  - D. chemotaxis

8. **Heparin, histamine and serotonin, which intensify inflammation are released by \_\_\_\_\_.**  
A. basophils  
B. eosinophils  
C. lymphocytes  
D. dendritic cells
9. **Lymphocytes that are effectors of cell-mediated immunity are called \_\_\_\_\_.**  
A. T-Cells  
B. B-cells
10. **T-cells mature in which of the following organs?**  
A. Spleen  
B. Liver  
C. Thymus gland  
D. Bone marrow
11. **Immune complex reactions are categorized into which type of immune hypersensitivity?**  
A. Type I  
B. Type II  
C. Type III  
D. Type IV
12. **The composition of undisturbed plaque changes from gram-positive coccoid and filamentous bacteria to gram-negative rods and spirochetes.**  
A. True  
B. False
13. **The bacterial pathogens most often associated with destructive periodontitis make up the \_\_\_\_\_ complex.**  
A. red  
B. orange  
C. blue  
D. green
14. **The primary pro-inflammatory cytokine is \_\_\_\_\_.**  
A. Prostaglandin E2  
B. Tumor Necrosis Factor  
C. Interleukin-1  
D. Interleukin-6
15. **The T-cell predominates in the \_\_\_\_\_ stage of periodontal disease.**  
A. initial  
B. early  
C. established  
D. advanced

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### Additional Resources

- No Additional Resources Available

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Dr. Mills is a Clinical Associate Professor with teaching responsibilities in the Postdoctoral Division of the Department of Periodontics, University of Texas Health Science Center, San Antonio. Prior to joining the faculty at UTHSCSA in 2000, Colonel Mills completed a distinguished 30-year career in the Air Force. Prior to his retirement, he served as the Chairman and Program Director of the United States Air Force Periodontics Residency at Wilford Hall Medical Center. He also held appointments as the Chief Consultant in Periodontics to the USAF Surgeon General and Special Consultant to the USAF Assistant Surgeon General for Dental Services. Dr. Mills received his dental degree from the University of Alabama School of Dentistry in 1970 followed by a one- year General Practice Residency at Eglin USAF Regional Hospital in Florida. From 1977 to 1980, he received his specialty training at Wilford Hall Medical Center, Lackland AFB, Texas and completed requirements for the Master of Science degree at the University of Texas Health Science Center, Houston.

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Dr. Kotsakis completed his residency in Periodontics and received his Masters of Science at the University of Minnesota where he first became interested in host-microbiome interactions in the oral soft tissue barrier. As a Clinician Scholar, he focuses on bone regeneration procedures in implant surgery and peri-implantitis therapy. In the lab, he conducts funded research across the spectrum of translational sciences from in vitro models to clinical trials. His current work is centered around identifying the biological mechanisms underlying peri-implant bone loss and developing novel treatments for dental and biomedical implants. He has published over 70 peer-reviewed articles and textbook chapters in high-impact journals, such as the Lancet, with more than 10,000 citations of his work. He is the recipient of multiple career and research awards from the American Academy of Periodontology, the Academy of Periodontology Foundation, and other organizations. He lectures frequently both nationally and internationally on implant surgical techniques, alveolar bone regeneration, and peri-implantitis therapy and he serves in the Editorial Review Boards of prestigious disciplinary and inter-disciplinary journals.

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