We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

6

Innate Immunite and Inflammation

Patrícia Abrahão and Dagmar Ruth Stach-Machado
University of Campinas
Brasil

1. Introduction

A bacterium can find in the human oral cavity a variety of environmental niches that provide the warmth, moisture and food necessary for growth. Bacteria are able to invade this environment, adhere and colonize, gain access to food sources, and escape clearance by host nonimmune and immune responses thanks to genetic traits they have acquired. Unfortunately, diseases can be caused by many of the mechanisms the bacteria use to maintain their niches. This can occur either by destroying the tissue directly or indirectly, since the surface structures of the bacteria stimulate strong inflammatory host responses which can/may be protective but are often the main causes of the disease symptoms.

The human body is colonized with numerous microbes as normal flora, many of which serve important functions for their hosts, such as protecting the host from colonization with pathogenic microbes. Therefore, not all bacteria cause disease. Almost 1000 microbial species have been identified in dental biofilm intimately integrated forming a consortia in which an interchange of nutrients and metabolic factors occurs. Genetic characteristics expressed by the biofilm let the microbial consortia to compete, cooperate, and survive a changing environment, resist antibiotics and acquire virulence factors to the detrimental of oral health.

A "*septic*" gingival inflammation occurs when microbes and their virulence factors compromise the junctional epithelium health. Some of the natural defense mechanisms and physical and chemical barriers are salivary pH, mucus, secretions containing antibacterial substances such as lysozyme and collectins, phagocytic cells as neutrophils, macrophages and natural killer cells, blood proteins, including the complement system and other inflammatory mediators such as cytokines that regulate and coordinate the innate immune response.. The role of these factors is to make it difficult for the bacteria to enter the body. However, bacteria often have the means to compromise the epidermal barrier and invade the body. Initially gram-positive bacteria infects the mouth, while peptidoglycan and its breakdown products, teichoic and lipoteichoic acids, are released, which induce a pyrogenic acute-phase responses. New Gram-negative species, such as *Porphyromonas gingivalis, Campylobacter rectus, Eikenella corrodens, Actinobacillus actinomycetemcomitans,* and oral *spirochetes (Treponema* species) may be found present in the biofilm in the first four days following the beginning of plaque accumulation. While the dental plaque formation continues, Gram-negative species become dominant over the Gram-positive species. The overgrowth of Gram-negative anaerobic bacteria is considered one of the main causative factors that induce a complex sequence of events known as the inflammatory response of gingivitis. The lipopolysaccharide (LPS) produced by gram-negative bacteria is an even

more powerful activator of acute-phase and inflammatory reactions and its lipid A portion is responsible for its endotoxin activity. Most bacterial components and structures binds to specific receptors on macrophages and neutrophils, the sentinel cells of the human body and crucial mediators of the inflammatory response. These cells can sense the non-self or pathogen-associated molecular patterns (PAMPs) through multiple membrane receptors such as Toll Like Receptors (TLR). The recognition through most TLR induces the activations and up regulated of the MyD88 dependent pathway that culminate with the phosphorylation of NF-kB and induction of the expression of the pro-inflammatory cytokines like TNF-α, IL-1β and IL-6 and prostaglandins. However, other pathways, which are independent of MyD88, may also be activated, using mainly TRIF as an adaptor molecule, with the purpose of regulating the first via secretion of anti-inflammatory cytokines, avoiding the progression of inflammation. There are several other classes of phagocyte receptors that bind microbes and mediate their internalization, such as mannose receptors that bind terminal mannose and fucose residues of glycoproteins and glycolipids. Scavenger receptors bind and mediate endocytosis of oxidized or acetylated low-density lipoprotein (LDL). Macrophage integrins, notably Mac-1, may also bind microbes for phagocytosis. G protein-coupled receptors, Fc and C3 receptors, and receptors for cytokines, mainly IFN-γ, function cooperatively to activate phagocytes to kill ingested bacteria. Phagolysosomes are formed by the fusion of phagocyte vacuoles with lysosomes, in which the microbicidal mechanisms, such as reactive oxygen intermediates (ROIs) (highly reactive oxidizing agents that destroy bacteria) are concentrated in bacteria. Besides ROIs, macrophages produce reactive nitrogen intermediates, mainly nitric oxide, by the action of an enzyme called inducible nitric oxide synthase (iNOS). Activated neutrophils and macrophages also produce several proteolytic enzymes in the phagolysosomes, which function is to destroy bacteria. One of the most important enzymes in neutrophils is elastase, a broad-spectrum serine protease known for being essencial to kill many types of bacteria. Endotoxin also stimulates the growth of B cells, and induces the expression of class II MHC molecules permits these cells to function as an antigen-presenting cell (APC). An example is a dendritic cell that acquires the antigen by phagocytosis or endocytosis and after the antigen is processed, the mature dendritic cells present it to TH cells. On the other hands, "*aseptic*" gingival inflammation can occur. Many factors can contribute for the development of this inflammation: drugs, hormones, autoimmunity diseases, and GVHD among other disorders.

2. Innate immunity and inflammation

Innate immunity can be seen to comprise four types of defensive barriers: anatomic, physiologic, phagocytic, and inflammatory.

2.1 The oral mucosal surfaces provide protective barriers against Infection

The physical and anatomic barriers that usually prevent the entry of pathogens are of distinct layers. The outer epithelial layer and underlying layer of connective tissue are the first line of defense against infection. IThese protect the deeper tissues (fat, muscle, nerve and blood supplies) from mechanical insults, such as trauma during chewing, and also prevents the entry of bacteria and some toxic substances into the body. The hard surface of some mucosa (such as the hard palate, the gingivae, and some areas on the dorsum of the tongue) is inflexible but resistant to abrasion, and is tightly bound to the underlying tissue.

The acquisition of organisms and the subsequent course of either stable colonization or invasion of the host involves complex host-parasite interactions. From one perspective, host factors are operative, appearing to select against certain species while being permissive to others. From another perspective, microbial species that are successful at colonization must overcome certain host factors to maintain a selective advantage and flourish within a particular body habitat. It is interesting to observe that while host mucosal defenses play a significant role contributing to the selection of the resident flora, it is this established flora that provides the host with what might be its most important local defense system. More than 1000 bacterial species or phylatypes have been detected in the oral cavity. These organisms are rarely involved in infection unless there is some breach of the mucosal surface or some upset in the balance of the normal flora. When this occurs, the host is susceptible to infection from both recently acquired organisms and those present before that may now become invasive resulting in the formation of microbial biofilms such as supre and subgingival dental plaque, and tongue surface debris, leading to dental caries, gingivitis, periodontal disease and oral malodor. The biofilm bacteria and their toxins perturb gingival epithelial cells as the first stage in a cascade of inflammatory and immune processes that lead to the destruction of gingival tissues and ultimately, in susceptible patients, alveolar bone loss and tooth loss as a result of periodontal disease.

2.2 Physiologic barriers to infection include general conditions and specific molecules

There are physiologic barriers that contribute to innate immunity such as pH, temperature, saliva containing antibacterial substances like lysozyme, collectins, complement system and proteins called cytokines, that regulate and coordinate many activities of the cells of innate immunity.

2.2.1 Saliva is the fluid present in the oral cavity that is produced by different salivary glands and its function is to protect the epithelial tissue against external harmful effects. The protection is achieved by the physical movement of exocrine glandular secretions that mechanically entrap and effectively remove many potentially harmful microorganisms and compounds. Its components, like lysozyme, collectins, blood proteins, complement system, soluble factors and secretory Immunoglobulin A can also bind to microorganisms inhibiting their adhesion to the mucosal surface. In addition, antibacterial mechanisms can influence the metabolism of bacteria by bacteriolysis, membrane damage, inhibition of growth, and cell killing. It is likely that besides the sharing of these general needs, the mucosal secretions also share a variety of protective components (Table 1).

2.2.2 A variety of **soluble factors /proteins** that are present in many different body fluids, including saliva, that are necessary to protect the oral epithelia from the large number of possible invading microbes and maintain the oral homeostasis of commensal and pathogenic bacteria. Moreover, the expression of anti-microbial proteins is differentially regulated by different periodontal pathogens (Handfield et al.2005) (Table 2), suggesting that a specific antimicrobial ''cocktail'' constitutes the physiological response to individual pathogens. This mix may also play a role in maintaining an appropriate balance between oral pathogens and commensals. **Histatins** are a family of several low molecular-weight histidine-rich peptides that are secreted mainly in parotid saliva and, to a lesser extent, in submandibular saliva. Histatins possess antimicrobial properties against a few strains of *Streptococcus mutans* and inhibit hemagglutination of the periopathogen *Porphyromonas*

Protective Funcions
Tissue coating (mucosal and tooth pellicle) Lubrification Humidification Remineralization of the teeth
Host Defense Functions
Immunological activity Anti-bacterial activity Anti-viral activity Anti-fungal activity
Digestion
Digestive enzymes Bolus formation Taste

Table 1. Functions of Human Salivary Secretions

gingivalis. In addition, histatins neutralize the endotoxic lipopolysaccharides located in the outer membranes of Gram-negative bacteria, which may be an important part of the host's defense system. Histatins are involved in functions that are specific of the oral cavity. Histatins 1, 3, and 5 bind to hydroxyapatite and may therefore be precursors of components of the acquired enamel pellicle. The formation of pellicle is the first step in dental plaqueformation. and an important participant in the mineralization dynamics of oral fluids. **Proline-rich proteins (PRPs)** are a heterogeneous group of proteins that comprise about 70% of the parotid proteins. PRPs are classified into three groups: acidic, basic and glycosylated. Hence, the acidic PRPs are involved in typical oral processes like mineral homeostasis and neutralization of toxic substances in the diet. Glycosylated basic PRPs function as masticatory lubricants and have also been shown to interact with several types of microorganisms such as *Fusobacterium nucleatum*. Basic PRPs have a more general protective function among all these proline-rich proteins. **Mucins** are proteins that give the typical visco-elastic character to all the mucosal secretions. In general, the physiological functions of the mucins include, among others, cytoprotection, lubrification, protection against dehydration, and maintenance of visco-elasticity in secretions. Human saliva contains two saliva-specific types of mucins, low and high-molecular-weight mucin glycoproteins, MG2 (150-200 kDa) and MG1 (>1000 kDa). MG1 adheres to the tooth surface, forming a barrier against acidic attacks, while MG2 binds to a large number of different microorganism, including *Candida albicans* and *Actinobacillus actinomycetemcomitans*. **Cystatins** belong to the class of cysteine proteinase inhibitors and their role is to regulate the activity of cathepsins, liberated during inflammatory reactions, e.g., in gingivitis and periodontitis. They are very important in the inhibition of several viruses presumably by blocking necessary cysteine proteinases, and may control the proliferation and invasion of tumor cells. **Secretory Immunoglobulin A (sig A)** is a member of the adaptive immune response and is the predominant immunoglobulin of the mucosal immune system.

Secretions of glands that are anatomically remote from the site of immunization, such as salivary glands, can contain sigA antibodies to antigens encountered through the oral cavity. In the same way, IgA-producing cells are induced by the common mucosal immune response, consisting of lymphoid tissues concentrated in special structures, such as Waldeyer's ring or pharyngeal lymphoid ring, which are anatomical terms describing the lymphoid tissue ring located in the pharynx and to the back of the oral cavity. It was named after the nineteenth century German anatomist Heinrich Wilhelm Gottfried von Waldeyer-Hartz. The ring consists of (from superior to inferior): Pharyngeal tonsil (also known as 'adenoids' when infected), tubal tonsil (where Eustachian tube opens in the nasopharynx), palatine tonsils (commonly called "the tonsils" in the vernacular, less commonly termed "faucial tonsils") and lingual tonsils. The protective role of sigA is via neutralizing antigens from viruses, toxins and enzymes, interact together with the innate immune factors (e.g., lysozyme, lactoperoxidase, lactoferrin). **Lysozyme**, a hydrolytic enzyme, is able to cleave the peptidoglycan layer and induce killing and lysis of the bacterial cell. **Kallikreins**, are a group of serine proteases that are found in glandular cells, neutrophils, and biological fluids, including saliva, and have a role in blood coagulation, via the activation of the Hageman factor. However, in saliva some hydrolysis of proline-rich proteins occurs by kallikrein. It has been implicated in the regulation of local blood flow in salivary glands, the processing of polypeptide hormones such as epidermal growth factor, in ion transport in epithelial cells, and neutrophil chemotaxis. **Collectins** are surfactant proteins that may kill certain bacteria directly by disrupting their lipid membranes or, alternatively, by aggregating the bacteria to raise their susceptibility to phagocytosis. **Extra-Parotid GlycoProtein (EP-GP)** is an acidic salivary glycoprotein of low molecular weight, 18-20 kDa, that can be localized only in the submandibular glands (in the serous acinar cells) and is absent from the parotid gland. It has been shown to have a strong affinity to hydroxyapatite and has a specific function in the oral cavity, e.g., as a component of the dental pellicle and modulation of oral microflora. **Albumin** is the most abundant protein present in serum plasma, constituting from 55 to 62% of the total serum proteins. In saliva of orally healthy individuals, albumin can be detected in only very small amounts. Salivary albumin concentrations are significantly increased in individuals with gingivitis or periodontitis Albumin is also found in a complexed form with proline-rich glycoprotein (PRG), and this complex, as a pellicle constituent, appears to play an effective role in lubrificating the oral tissue surfaces. **Calprotectin** is a protein that inhibits bacterial growth by acting as divalent cation scavengers. **Secretory leucocyte protease inhibitor and elastase-specific inhibitor** present in the human submandibular gland and saliva exhibit anti-elastase activity and can kill both Gram-negative and Gram-positive bacteria. **Beta-2-microglobulin** causes agglutination of *S. mutans* in the presence of calcium. **Fibronectin** is a glycoprotein that is expressed in hepatocytes, epithelial cells and other cells, and is present in saliva. The protein induces bacterial agglutination and plays a role in reducing bacterial adhesion to oral surfaces. Fibronectin also binds directly to fimbrillin from *P. gingivalis* inhibiting the fimbrillin induced expression of inflammatory cytokines in macrophages. **Lactoperoxidase and myeloperoxidase** form the principal components of the peroxidase system of saliva. The enzymes catalyse the oxidation of thiocyanate ions (SCN) by hydrogen peroxide, and the reaction product hypothiocyanite (OSCN) is bactericidal. Hydrogen peroxide-mediated oxidation of chloride and iodide produces further bactericidal reaction products.

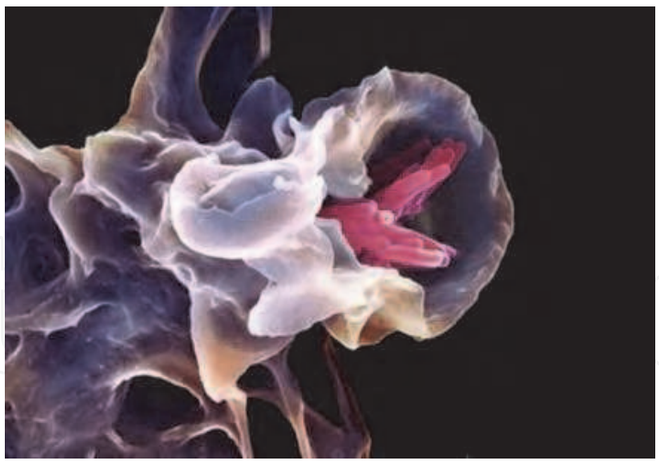
2.2.3 The **antimicrobial peptides** are necessary to protect the oral epithelia from the large number of possible invading microbes and maintain the oral homeostasis of commensal and pathogenic bacteria. Moreover, the expression of anti-microbial proteins is differentially regulated by different periodontal pathogens (Handfield et al. 2005), suggesting that a specific antimicrobial ''cocktail'' constitutes the physiological response to individual pathogens. This mix may also play a role in maintaining an appropriate balance between oral pathogens and commensals. Antimicrobial peptides exhibit striking variation in their ability to kill different species of oral bacteria (Gram-negative and Gram-positive) or different strains of the same species, as well as against yeast and viruses. In humans these antimicrobial peptides include defensins, adrenomedullin, cathelicidin (family member LL-37 in skin and oral mucosa and other epithelia), statherin and azurocidin. **Defensins** exhibit broad antibacterial activity to both gram-positive and gram-negative bacteria. The peptides bind to or are inserted into the bacterial cell membrane, causing membrane permeabilization and cell lysis. Defensins are most active against negatively charged phospholipids and increased salt concentrations inhibit their activity, suggesting that ionic interactions between membrane lipids and the cationic peptide are involved in their activity. The human defensins include the α-defensins. Alpha-defensins are expressed in neutrophils and have been identified in the gingival crevicular fluid of both healthy and diseased sites. Beta-defensins are found in gingival epithelial cells and whose expression is correlated with cellular differentiation and is regulated by calcium and phospholipase D. **Adrenomedullin** is a cationic amphipathic peptide with one disulfide bond. It is found in gingival crevicular fluid and glandular and whole saliva. In gingival crevicular fluid, the amount of adrenomedullin is about twice as high in periodontal disease sites than in healthy sites. **Cathelicidin,** precursor of the antimicrobial peptides FALL-39 and LL-37. LL-37, is a cationic alpha-helical peptide, and is expressed by neutrophils, epithelial cells, and can be found in saliva and gingival crevicular fluid. In addition to antibacterial activity, LL-37 also binds to and neutralizes lipopolysaccharide from gram-negative bacteria. In Candida albicans, the peptide causes disintegration of the plasma membrane. **Statherin** is found in gingival crevicular fluid and saliva. The peptide is secreted by the parotid and submandibular glands and inhibits the crystallization of calcium phosphate but also inhibits growth of anaerobic bacteria isolated from the oral cavity. It is the C-terminal peptide of statherin that exhibits the antibacterial effect**. Azurocidin** is expressed in azurophil granules of neutrophils present in human saliva and is antibacterial to gram-negative bacteria, presumably because of a strong affinity for lipopolysacchaide.

2.2.4 The **Complement system consists of a** group of zimogen serum proteins that can be activated through a variety of specific and nonspecific immunologic mechanisms. These mechanisms change the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either by lysis of the pathogens or facilitating their clearance. Complement may function as an effector system that is set off by binding of antibodies to certain cell surfaces, or it may be activated by reaction between complement molecules and certain components from microbial cell walls. Reactions between complement molecules or fragments of complement molecules and cellular receptors set off activation of cells of the innate or adaptive immune systems. When periodontal tissues become inflamed, serous exudates begin to appear that mix with the salivary secretions at the gingival margin. The serous exudates contain a functional complement system, and the saliva secretions appear to cooperate and indeed potentiate the

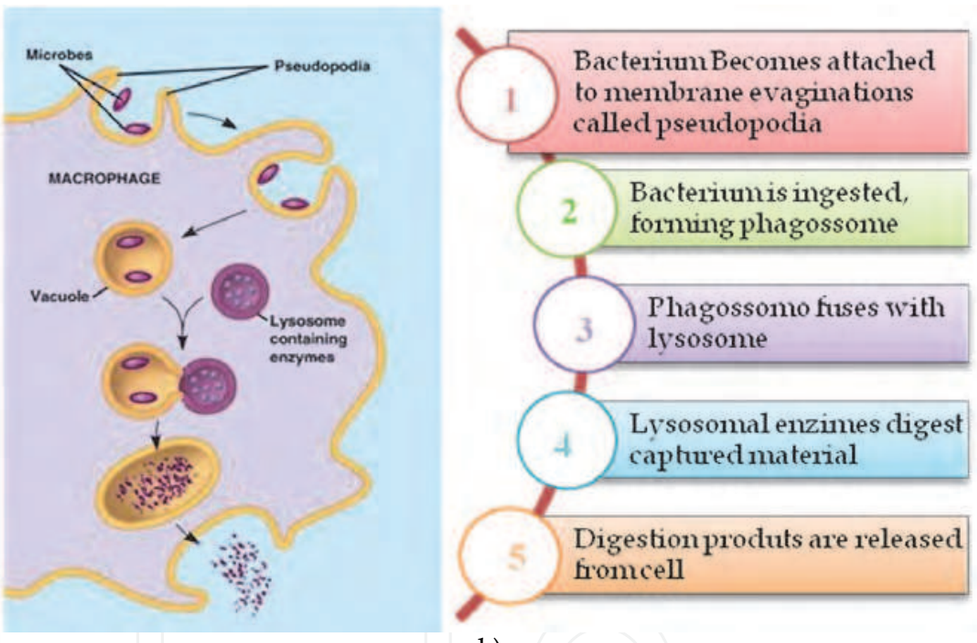
complement system. Salivary secretions containing complement-reactive substances have the potential to cooperate in potentiating the activation of the classic and alternative complement pathways with enhanced C4b and C3b deposition, such as secretory IgA and high-molecular-weight nonimmunoglobulin agglutinins (NIA). Secretory IgA, when aggregated, activates the alternative complement pathway, while the aggregation of NIA, activate C1, causing C4 conversion and C4b deposition. Since NIA interacts with C1 and with immune complexes whichnot only involving secretory IgA but also IgG and IgM immune complexes. For that reason, NIA may have a role in (1) mediating activation of the classic complement pathway by secretory IgA and (2) enhancing the effectiveness of complement activation and deposition once serum or serous exudates contact human saliva. Proteins of the complement are low levels of gingival crevicular fluid (GCF) are present in health, the flow rate of this complement containing fluid dramatically increases as a consequence of the inflammation of periodontal tissues. In summary, human salivary secretion tend to potentiate the serum complement system. Dental plaque, and microorganisms in dental plaque activate the classic and the alternative complement pathways. Enhancement of C1q, C4b and C3b deposition by saliva-complement interactions occurring at supragingival margin may aid in the elimination of oral microbes in that area. A reversal of these enhancing effects might occur if certain bacteria, which are strong protease producers, colonize the dental plaque and digest residual native complement components and the C4b and C3b deposited on the microbial surfaces.

3. Cells that ingest and destroy pathogens make up a phagocytic barrier to infection

Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages (MØ), which are present in large numbers at portals of entry from the outside environment, just as within the oral cavity, which are constantly exposed to foreign particles (e.g., amalgam), viruses, bacteria, and fungi. Epithelial oral MØ express high levels of PRR including Toll-like receptors (TLR) and families of cytosolic proteins (e.g., NODs, NALPs), scavenger receptors (SR), mannose receptors (M R), G protein-coupled receptors, Fc and C3 receptors. MØ also express receptors for cytokines, mainly IFN-γ, which function cooperatively to activate phagocytes to kill ingested bacteria. Natural ligands on gram-positive bacteria that initially infect the mouth include peptidoglycan and their breakdown products, teichoic and lipoteichoic acids, which are released and stimulate toxin-like pyrogenic acute-phase responses. The lipopolysaccharide is produced by gram-negative bacteria is an even more powerful activator of acute-phase and inflammatory reactions. The lipid A portion of lipopolysaccharide is responsible for endotoxin activity. For TLRs to transmit signals via adaptor molecules selectively they depend on other surface molecules such as CD14/MD2 and C-type lectin-like receptors for proximal ligand binding and recognition. Collaboration among different membrane receptor families, as well as with nonclassical opsonins and proteinase cascades such as complement, is likely to be an important mechanism to enhance affinity of binding and specificity. The surface receptors of the MØ regulate a scope of functions, such as differentiation, growth and survival, adhesion, migration, phagocytosis, activation, and cytotoxicity. Their ability to recognize a wide range of endogenous and exogenous ligands, and to respond appropriately, is central to MØ functions in homeostasis as well as host defense in innate and acquired immunity, autoimmunity, inflammation, and immunopathology.



a)



b)

Fig. 1. (a) Macrophage engulfing TB bacteria. Colored scanning electron micrograph (SEM) of a macrophage white blood cell (purple) engulfing a tuberculosis (Mycobacterium tuberculosis) bacterium (pink). This process is called phagocytosis. Macrophages are cells of the body's immune system. They phagocytose and destroy pathogens, dead cells and cellular debris. Credit: SCIENCE PHOTO LIBRARY (b) Schematic diagram of the steps in phagocytosis of a bacterium. [Part a, www. Nicerweb.com]

4. Inflammation represents a complex sequence of events that stimulates immune responses

4.1 Septic gingival inflammation

Tissue damage by microorganisms in gingival plaque induces a complex sequence of events collectively known as the inflammatory response. There is individual variation in this

response with some individuals taking longer to manifest disease compared to others. So, while it has been known for many years that plaque is the etiological agent, the factors contributing to patient susceptibility, for example, innate individual susceptibility, may involve both host-related genetics and the nature of the microbial challenge (the biofilm specific antigens involved in periodontal disease and of the immune response to them). Innate immunity is a consistent feature of both gingivitis and periodontitis. Strong innate immune responses, with high levels of IL-12, are associated with a Th1 response, while poor innate immune responses are suggested to favor a Th2 response. All individuals with dental plaque will advance to gingivitis, and not all individuals will progress to periodontitis. The advancement from health to gingivitis and then to periodontitis can be loosely divided into four stages: initial, early, established and advanced lesions.

4.1.1 The initial stage occurs almost immediately after toothbrushing. Some minutes after brushing your teeth, saliva derived glycoprotein deposits start to cover the tooth surface with what is referred to as "pellicle". The formation of pellicle is the first step in dental plaque formation. The pellicle is then colonized by Gram-positive bacteria such as *Streptococcus sanguis*, *Streptococcus mutans*, and *Actinomyces viscosus,* becoming what is known as dental plaque. Bacteria cells interact with pellicle components enabling plaque to firmly adhere to the tooth surface (Figure 2). Substances produced by the already accumulated bacteria enrich the plaque environment making it favorable for the growth of other species of bacteria. The presence of pathogenic bacteria is necessary but not sufficient for this process. The host immune and inflammatory response to the microbial challenge is a critical determinant of susceptibility to develop the destructive disease, and is under the influence of multiple behavioral, environmental, and genetic factors.

During the first four days of plaque accumulation, new Gram-negative species, such as *Porphyromonas gingivalis, Campylobacter rectus, Eikenella corrodens, Actinobacillus actinomycetemcomitans,* and oral *spirochetes* (*Treponema* species) can be found in the plaque biofilm. On the following days, Gram-negative species become dominant over the Gram-positive species. The overgrowth of Gram-negative anaerobic bacteria is considered one of the main causative factors that induce a complex sequence of events known as the inflammatory response of gingivitis. As plaque accumulates, bacterial enzymes and metabolic end products increase the permeability of the junctional epithelium, allowing both the ingress of further bacterial products and, at the same time, the outflow of gingival fluid.

This gingival fluid is essentially a serum product, which contains all the components of complement. Activation of complement via the so-called ‘‘alternative pathway’’ in the gingival sulcus results in production of the anaphylatoxins C3a and C5a, which in turn lead to the release of vasoactive amines from mast cells. These vasoactive substances lead to an increase in vascular permeability facilitates influx of fluid and polymorphonuclear leukocytes (PMNs) from the capillaries into the gingival sulcus and the formation of edema.

Macrophages are known to secrete TNF-α and IL-1β in response to serial stimulation with lipopolysaccharide (LPS). Caspase 1 activation by inflammasome complexes in response to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) induces the maturation and secretion of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-18 and IL-33. Both IL-1β and IL-18 are highly potent proinflammatory cytokines. IL-18 induces interferon γ expression and secretion from IL-12-primed naïve T cells to promote the differentiation of type 1 helper T cells. IL-33 has recently

been identified as the ligand of the IL-1 receptor family protein ST2 and promotes responses mediated by type 2 helper T cells. Upon cleavage of their proforms by caspase-1, these cytokines become active and are secreted. Thus, caspase-1 activity is critical for the inflammatory response. The release of DAMPs is a common event, as tissue damage and cell lysis are often associated with infections and lead to the release of host molecules. The importance of the recognition of these DAMPs by the immune system is that it not only allows the sensing of an ongoing infection and subsequent recruitment of more immune cells, but also can initiate the repair of the damaged tissue. It seems, then, that the innate immune pathway not only scans the cellular environment for signs of invading pathogens, but also recognizes the damage caused by them. Cytokines such as tumor necrosis factor and IL1 simulate IL8 synthesis which is also a potent chemoattractant for neutrophils.

The emigration of phagocytes is a multistep process that includes adherence of the cells to endothelial wall of the blood vessels (margination), followed by their emigration between the capillary-endothelial cells into the tissue (diapedesis or extravasation), and finally, their migration through the tissue to the site invasion (chemotaxis). This event is initiated by a variety of chemical mediators, some derived from bacteria, others generated by several plasma enzyme systems, and some others from products of various white blood cells. The mast cells release preformed tumor necrosis factor-a (TNF-a), which is largely responsible for the expression of adhesion molecules by endothelial cells (e.g., ELAM-1, ICAM-1). Combined with an increase in Interleukin-8 (IL-8) production by the epithelial cells, which helps establish a fast flow of PMNs through the junctional epithelium and the subsequent sticking and migration of PMNs. In addition, the presence of of neutrophil mediators, including leukotriene B4, platelet activating factor, thromboxane B2, elastase, and collagenase into the gingival sulcus contribute to the process. (Figure 3). Once in the gingival sulcus, however, the PMNs are unable to phagocytosis the bacteria.

Clinically, gingival inflammation is characterized by gingival redness, swelling and increased tendency of bleeding of the soft tissue.

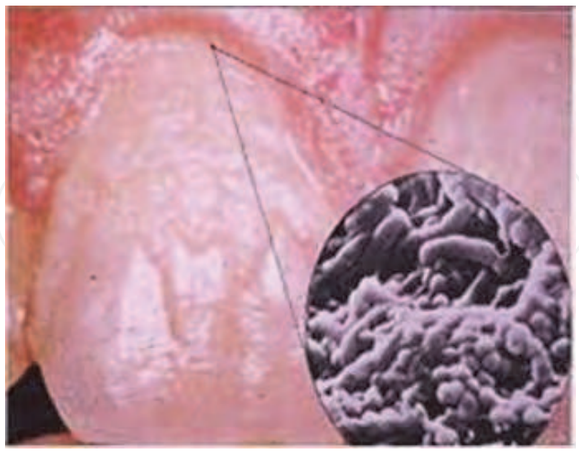
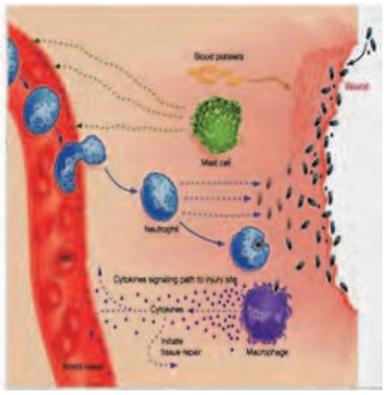
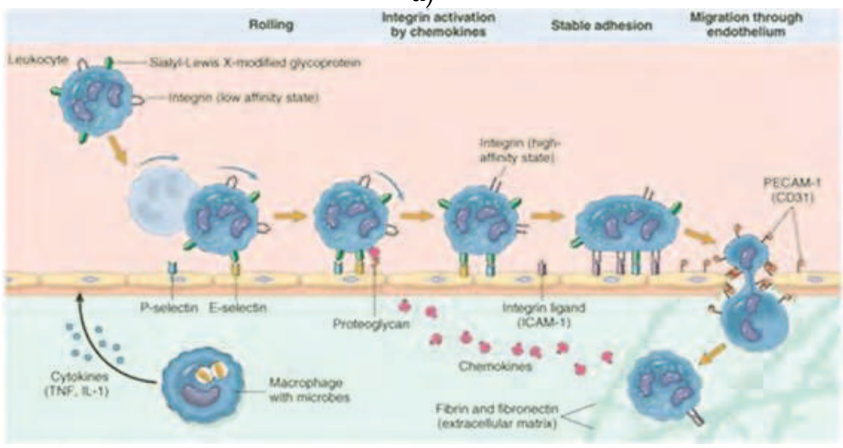


Fig. 2. Dental plaque formation, saliva derived glycoprotein deposits start to cover the tooth surface with what is referred to as "pellicle". The formation of pellicle is the first step in dental plaque formation. The pellicle is then colonized by Gram-positive and Gran-negative bacteria that interact with pellicle components enabling plaque to firmly adhere to the tooth surface.



a)



b)

Fig. 3. (a) Bacteria adhere the surface of gingiva. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases. Neutrophils secrete factors that kill and degrade pathogens. Macrophages secrete cytokines that attract immune system cell to the site and activate cells involved in tissue repair. (b) Rolling, margination and adhesion of neutrophils: interaction between selectins, integrins and cell adhesion molecules like VCAM. These process by diapedesis are madee for chemokines, bacterial peptides, C5a, LTB4 (Leukotreine), IL 8(interleukin). Actin myosin interactions in the leucocyte are responsible for, transmigration by diapedesis. (Figures of link: http://medicinembbs.blogspot.com/2011/02/inflammation.html)

4.1.2 The early lesion or stable lesion. At approximately 4–7 days of plaque accumulation, the nature of the developing lesion changes from one consisting primarily of PMNs to one with increased numbers of lymphocytes and macrophages. This is the early lesion in which vascular changes can be better observed, as illustrated by the activation of previously dormant capillary beds, and the development of perivascular inflammatory infiltrates below the junctional epithelium. The result is a net increase in the flow of fluid into the affected gingival tissues, and, after that, an increase in the flow of gingival crevicular fluid. Further concurrent widening of intercellular spaces between the epithelial cells of the junctional epithelium allows increased diffusion of bacterial products into the gingival tissues and escalation of the inflammatory response. The lesion begins as small perivascular infiltrates which progressively enlarge and conflate until they become clinically evident at around day 12 to 21. By day 21, lymphocytes make up 70 per cent of the infiltrate. As noted above,

gingivitis develops as perivascular lymphocyte/macrophage lesions. Increasing in size, they conflate and merge together, eventually becoming clinically evident**.** The lymphocytes are predominantly T cells with a CD4:CD8 ratio of around 2:1. Increased numbers of Langerhans cells are seen in the oral as well as oral sulcular epithelium. While interdigitating dendritic cells can be found in the perivascular spaces, the majority of macrophages in the developing lesion are acid phosphatase positive phagocytic cells. As soluble antigen enters the tissues, it is taken up by the resident Langerhans cells and carried to the regional lymph nodes where antigen specific T cells are sensitized. These sensitized cells then travel back to the site of original antigen challenge (i.e., the gingival tissues). Following further antigen presentation by dendritic cells, they are activated and control, together with the infiltrating phagocytic macrophages, the ingress of antigen and achieve a balance with the plaque biofilm. The various phagocytes (PMNs in the gingival sulcus and macrophages in the tissues) are unable to eradicate the microbial challenge, for plaque bacteria seldom invade the host tissues. The subsequent, prolonged nature of the inflammatory response results in gingivitis becoming chronic in nature. While in most people the immune response is able to contain the microbial challenge, it is only with mechanical cleaning that the microbial challenge can be eradicated. Collagen is degraded in the stable lesion but there is no loss of attachment. When the plaque is removed, gingival tissues repair and remodel, and there is no permanent damage or alteration of tissue architecture.

4.1.3 The established or progressive lesion. In some people, either due to environmental factors or their own innate susceptibility, or both, the stable lesion changes to a B cell / plasma cell response with the production of high levels of Interleukin-1 (IL-1) and Interleukin-6 (IL-6) and subsequent connective tissue breakdown and loss of bone. As the connective tissue attachment to the tooth breaks down, the junctional epithelium migrates in an apical direction and a periodontal pocket forms, which becomes lined by pocket epithelium with in-growth of rete pegs into the surrounding connective tissue. Increased permeability of this pocket epithelium allows continued ingress of microbial products, the continued production of inflammatory cytokines such as IL-1, TNF-a, Prostaglandin E2 (PGE2), leukotrienes, and chemokines, and perpetuation of the inflammatory process leading to continued tissue destruction. The main identifying feature of the progressing, established lesion is the predominance of plasma cells within the periodontal connective tissues indicative of a B cell adaptive immune response.

4.1.4 The advanced lesion. The main difference between the advanced and the established lesions is the overt loss of attachment that is evident clinically and histologically. It is now generally accepted that the mechanism of tissue destruction is via the effects of the immune response. Fibroblasts and macrophages are stimulated by the inflammatory cytokines IL-1, TNF-α and PGE_2 to produce matrix metalloproteinases (MMP), which are a family of proteinases whose primary purpose is the degradation of the extracellular matrix. Collagen molecules are cleaved into smaller fragments, which then become denatured in the extra-cellular environment or are phagocytosed by surrounding fibroblasts. With the advancement of the lesion, alveolar bone loss becomes apparent. However, a non-infiltrated fibrous band remains adjacent to the crystal bone, which effectively encapsulates the progressing lesion. With advanced periodontitis, plasma cells occupied 31% of the lesion volume, while the proportion of lymphocytes varied between 5% and 10%. Macrophages and polymorphonuclear (PMN) cells were found in densities of 1–2% and fibroblasts in 5%. Thus, the volume occupied by plasma cells was three times larger than the proportion of lymphocytes. Other inflammatory cells occurred only in small numbers (figure 4), containing substantial numbers of immunoglobulin (IgG, IgM).

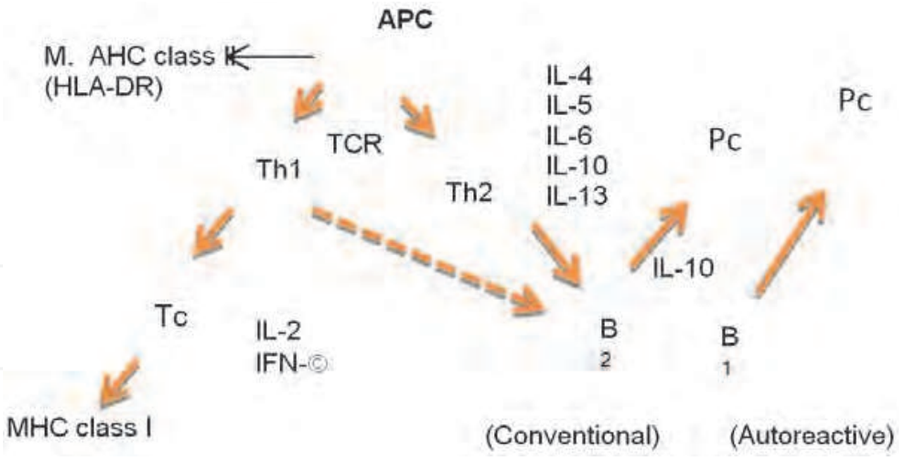


Fig. 4. Schematic outline of regulatory components of adaptive host response in periodontitis.

5. Conclusion

Treatment planning in gingivitis, as with any disease, must be based on an understanding of the aetiology and pathogenesis of the disease. While plaque is the cause of the disease, it is the innate susceptibility of the host that determines the ultimate outcome of the disease process. Innate susceptibility, in turn, is determined by the nature of the immune response to the specific periodontopathic complexes comprising the plaque biofilm. The innate immunity include physical barriers, such oral mucous, as well as the production of lysozyme, collectins, blood proteins, secretory Immunoglobulin, complement components, cytokines, adhesion, chemokines and others substances that regulate and coordinate many activities of the cells of innate immunity. The elimination (if possible) of any known cause of increased susceptibility and improvement in oral hygiene leads to the decrease of the dental plaque, which is responsible for the inflammatory alterations. Products containing antiseptics such as chlorhexidine or triclosan are effective against both gram-positive and gram-negative bacteria and reduced likelihood of gingivitis progressing to periodontitis, arrest progression of periodontitis, prevent supragingival calculus, and reduce oral malodor. Most self-administered plaque control programs are ineffective unless periodic professional reinforcement is also provided; a single session of ultrasonic prophylaxis associated with oral hygiene instructions is an effective method of reversing gingivitis, reducing bleeding upon probing, as well as the subgingival microflora. Through constant flushing activity during sonic instrumentation, disrupting the bacterial cell.

6. References

Amunulla A *et.al.* (2008)Lymphocyte subpopulation in healthy and diseased gingival tissue. *J Indian Soc Periodontol*. May;12(2):45-50.

Champagne CM *et.al* (2003) Potential for gingival crevice fluid measures as predictors of risk for periodontal diseases. *Periodontol 2000.* 31:167-80.

Cortelli SC *et al.* (2010). Self-performed supragingival biofilm control: qualitative analysis, scientific basis and oral-health implications. *Braz Oral Res.*44 24(Spec Iss 1):43-54.

Cullinan MP *et al.* (2003). Acquisition and loss of Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and Prevotella intermedia over a 5-year period: effect of a triclosan/copolymer dentifrice. *J Clin Periodontol*. 30:532–541.

den Hertog AL *et al.* (2005). Candidacidal effects of two antimicrobial peptides: histatin 5 causes small membrane defects, but LL-37 causes massive disruption of the cell membrane. *Biochem J.* 388: 689–695.

Denny P et al. (2008). The Proteomes of human parotid and submandibular / sublingual gland salivas collected as the ductal secretions. *J Proteome Res,* 7: 1994–2006.

Diamond, G *et al*. (2009). The roles of antimicrobial peptides in innate host defense. *Current Pharmaceutical Design.* 15, 2377–2392.

Ebersole JL, Cappelli D & Holt SC (2001). Periodontal diseases: to protect or not to protect is the question? *Acta Odontol Scand.* 59(3):161-6. Review

Ganz T (2005). Defensins and other antimicrobial peptides: a historical perspective and an update. *Comb Chem High Throughput Screen.* 8: 209–217.

Giannobile *et al.* (2009) Saliva as a diagnostic tool for periodontal disease: currentstate and future directions. *Periodontology 2000.* 50,52–64.

Gürses N *et al.* (1996). Immunohistochemical characterization of lymphocyte subsets in chronic adult periodontitis. *J Nihon Univ Sch Dent.* 38(2):94-101.

Hannigan E *et al.* (2004). Soluble cell adhesion molecules in gingival crevicular fluid in periodontal health and disease. *J Periodontol*. 75(4):546-50.

Ihalin R, Loimaranta V & Tenovuo J (2006). Origin, structure, and biological activities of peroxidases in human saliva. *Arch Biochem Biophys,* 445: 261–268.Novaes Júnior AB *et al*. (2004). Control of gingival inflammation in a teenager population using ultrasonic prophylaxis. *,* 15(1):41-5.

Kinane DF & Lappin DF (2001). Clinical, pathological and immunological aspects of periodontal disease. *Acta Odontol Scand.* 59(3):154-60. Review

Kinane DF & Lappin DF (2002). Immune processes in periodontal disease: a review. *Ann Periodontol*. 7(1):62-71.

Kochanska *et al.* (2000). The effect of statherin and its shortened analogues on anaerobic bacteria isolated from the oral cavity. *Acta Microbiol Pol,* 49: 243–251.

Lamkanfi M (2011). Emerging inflammasome effector mechanisms. *Nat Rev Immunol.* 11(3):213-20.

Llena-Puy MC, Montanana-Llorens C & Forner-Navarro L (2004). Optimal assay conditions for quantifying fibronectin in saliva. *Med Oral,* 9: 191–196.

Lundy FT *et al.* (2006). Radioimmunoassay quantification of adrenomedullin in human gingival crevicular fluid. *Arch Oral Biol.* 51: 334–338.

Murakami *et al*. (2002).Cathelicidin antimicrobial peptides are expressed in salivary glands and saliva. *J Dent Res.* 81: 845–850.

Nakajima T *et al.* (2005). Regulatory T-cells infiltrate periodontal disease tissues. *J Dent Res.* 84(7):639-43.

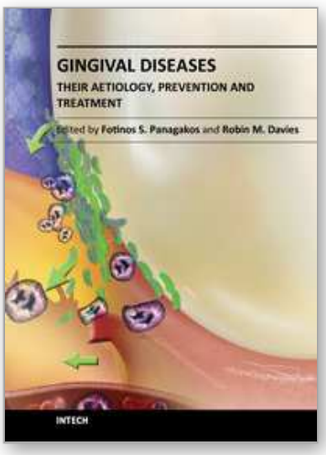
Neville BW *et.al.* (2002). *Oral & Maxillofacial Pathology*, ed 2, Philadephia, WB Saunders.

Nishikawa M *et al.* (2002), Yamaguchi Y, Yoshitake K, Saeki Y. Effects of TNFalpha and prostaglandin E2 on the expression of MMPs in human periodontal ligament fibroblasts. *J Periodontal Res*.37:167–176.

Ohlrich EJ, Cullinan MP & Seymour GJ(2009). The immunopathogenesis of periodontal disease. *Australian Dental Journal.* 54:(1 Suppl): S2–S10.

van Gils PC *et al.* (2003). Salivary cystatin activity and cystatin C in experimental gingivitis in nonsmokers. *J Clin Periodontol*. 30: 882–886.

vanderSpek JC *et al*. (1989). Localization of the genes for histatins to human chromosome 4q13 and tissue distribution of the mRNAs. *Am J Hum Genet*45: 381–387.



Gingival Diseases - Their Aetiology, Prevention and Treatment
Edited by Dr. Fotinos Panagakos

ISBN 978-953-307-376-7
Hard cover, 230 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

Gingival diseases are a family of distinct pathological entities that involve the gingival tissues. These signs and symptoms of these diseases are so prevalent in populations around the world that they are often considered to be â€œnormalâ€ features. The diseases are now classified into two main groups namely: Plaque-Induced and Non-Plaque Induced Gingival Diseases. This book provides dentists, dental hygienists, dental therapists and students with a comprehensive review of gingival diseases, their aetiology and treatment.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Patrícia Abrahão and Dagmar Ruth Stach-Machado (2011). Innate Immunite and Inflammation, Gingival Diseases - Their Aetiology, Prevention and Treatment, Dr. Fotinos Panagakos (Ed.), ISBN: 978-953-307-376-7, InTech, Available from: http://www.intechopen.com/books/gingival-diseases-their-aetiology-prevention-and-treatment/innate-immunite-and-inflammation

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen