Chapter

Pathogenesis of Gingivitis

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Abstract

The 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Condition identified the gingivitis case by the presence of gingival inflammation at one or more sites and agreed upon bleeding on probing as the primary parameter for diagnosis of gingivitis. Clinical gingival health is generally associated with an inflammatory infiltrate and a host response consistent with homeostasis. The molecules that play a role in the pathogenesis are divided into two main groups: those derived from the subgingival microbiota (i.e., microbial virulence factors) and those derived from the host immune-inflammatory response. The immune system is essential for the maintenance of periodontal health and is categorized as innate immune system and the adaptive immune system. Innate immunity reflects the capacity of the host to defend against infectious attacks. Understanding the disease processes is important for the development of improved treatment strategies.

Keywords: pathogenesis, immune response, host susceptibility, inflammatory mediators

1. Introduction

Chronic gingivitis and periodontitis are chronic inflammatory lesions which display stages of inflammation as well as healing. The 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Condition identified the gingivitis case by the presence of gingival inflammation at one or more sites and agreed upon bleeding on probing as the primary parameter for diagnosis of gingivitis [1, 2]. Clinical gingival health is generally associated with an inflammatory infiltrate and a host response consistent with homeostasis.

The role of the immune response in periodontal destruction independent of bacteria was first described by Ivanyi et al. [3]. Later, Taubman et al. [4] studied the role of the immune response in a germ-free rat model of experimental periodontal disease and concluded that in order to control the disease, it would be crucial to enhance the protective "arm" of the immune response and suppress its destructive aspect [4]. The molecules that play a role in the pathogenesis are divided into two main groups: those derived from the subgingival microbiota (i.e., microbial virulence factors) and those derived from the host immune-inflammatory response. Even though "periopathogenic bacteria" are still regarded as the main initiating agents, immune-inflammatory response of the host to these pathogens plays an important role in the pathogenesis of PD [5].

2. Histopathology of gingivitis

The plaque biofilm causes most of the injury to the periodontal tissue through indirect mechanisms dependent on initiation and propagation of inflammatory host tissue reactions. The development of gingivitis is mainly the infiltration of the connective tissues by numerous defense cells, particularly neutrophils, macrophages, plasma cells, and lymphocytes. The accumulation of these defense cells and the extracellular release of their destructive enzymes cause destruction of collagen and subsequent proliferation of the junctional epithelium leading to vasodilatation, increased vascular permeability, and hyperplastic gingival tissues. Clinically it appears as erythematous and edematous gingiva: the clinical appearance of gingivitis. The classic studies of Page and Schroeder [6] described the basic understanding of histologic changes that occur in the gingival tissues as the initial, early, established, and advanced gingival lesions. These are histologic descriptions only, primarily based on findings in experimental animals.

2.1 The initial lesion

The initial lesion develops within 2–4 days of the accumulation of plaque at a site free of plaque biofilm, which is evident microscopically since the gingival tissues always have characteristics of a low-grade chronic inflammatory response as a result of the continual presence of the subgingival biofilm. In other words, the initial lesion corresponds to the histologic picture that is evident in clinically healthy gingival tissues. This low-grade inflammation characterized by vasodilatation and increased vascular permeability along with upregulation of intercellular adhesion molecule-1 (ICAM-1) and E-selectin in gingival vasculature facilitates migration of neutrophils and monocytes into the connective tissue. This influx of fluid flow from the vessels increases the hydrostatic pressure in the local microcirculation resulting in increased gingival crevicular fluid (GCF) flow.

2.2 The early lesion

The early lesion corresponds to the early clinical signs of gingivitis and characterized by erythematous clinical appearance of gingiva due to proliferation of capillaries and vasodilatation [7]. The predominant infiltrating cell types are neutrophils and T lymphocytes [7]. The basal cells of these epithelial structures proliferate apically resulting in edema of gingival tissues and deepening of gingival sulcus. The subgingival biofilm proliferates apically in this ecologic environment rendering plaque control difficult in these areas. The early gingival lesion may persist indefinitely, or it may progress further.

2.3 The established lesion

The established lesion corresponds to clinical appearance referred to as “chronic gingivitis” and depends on many factors, such as composition and quantity of the plaque biofilm, host susceptibility factors, local and systemic risk factors. A study by Page and Schroeder [6] defined established lesion as mainly dominated by plasma cells with inflammatory cell infiltrate in connective tissues and destruction of collagen fibers. Neutrophils accumulated in the tissues, which are also a major source of matrix metalloproteinase-8 (MMP-8; neutrophil collagenase) and MMP-9 (gelatinase B), release their lysosomal enzymes in the inflamed gingival tissues causing destruction of collagen bundles. This is followed by deepening of sulcus and formation of ulcerated pocket epithelium along the tooth surface resulting

in bleeding on probing which is a common feature of chronic gingivitis. These inflammatory changes are still completely reversible if effective plaque control is reinstituted.

2.4 The advanced lesion

The advanced lesion, as described by Page and Schroeder [6], marks the transition from gingivitis to periodontitis which is determined by many factors, such as composition and quantity of the biofilm, the host inflammatory response, and environmental and genetic risk factors.

3. Host susceptibility

The tooth has a unique situation in the mammalian biology and presents a special challenge to the immune system [8]. The marginal gingiva includes the epithelial and connective tissue attachment apparatus that provides a biological seal between the tooth and the gingival soft tissues.

The oral cavity is a unique microenvironment where millions of bacteria live in harmony with our host defense mechanisms, with the bacterial host balance maintained by the amount of bacterial load through our regular oral hygiene practices. It is therefore important to understand the cellular and molecular elements involved in the pathways from health to disease and from disease to repair and regeneration.

3.1 Role of host susceptibility in gingivitis

Even though the development of gingivitis after plaque accumulation is a universal finding, the rate or speed of development and the degree of the clinical inflammatory response are variables between individuals, even under similar plaque accumulation conditions [9]. The studies recognizing the role of host contributing to the pathology of periodontal disease was a major breakthrough [10]. Various studies using the experimental gingivitis model showed 13% of all individuals representing a "resistant" group [9, 11, 12]. The factors modulating the appearance of gingival inflammation in response to plaque accumulation are mainly exacerbated gingival response to plaque, including metabolic factors such as puberty and pregnancy; genetic factors such as Down syndrome; nutritional factors such as vitamin C deficiency; the intake of drugs such as those leading to gingival enlargement; systemic diseases such as leukemia, immune deficiencies, and diabetes mellitus; and other conditions such as stress [9].

Gingivitis and periodontitis are the result of a coordinated action of clearly defined cellular players (proinflammatory and anti-inflammatory), which communicate with each other [13]. An inflammatory reaction can develop in two directions, either being destructive or regenerative depending on the bacterial antigen load and properties. If destructive, the innate immune reaction is followed by an adaptive or specific immune response, associated with the loss of tissue structure to create space for the immune process, and resolution of inflammation is associated with the regeneration of these structural hard and soft tissue components. It is therefore important to understand the cellular and molecular elements involved in the pathways from health to disease and from disease to repair and regeneration. The complex biological mechanisms occur in many phases from bacterial biofilm formation to periodontal regeneration and repair.

3.2 Host cells in periodontal pathogenesis

The inflammatory infiltrate of periodontal disease (gingivitis and periodontitis) is characterized by polymorphonuclear leukocytes (PMNs), macrophages, lymphocytes, plasma cells [6]. The periodontium consists of cellular elements (epithelial cells, the periodontal ligament and gingival fibroblasts, and osteoblasts and osteoclasts) and molecular elements (extracellular matrix components such as the various collagens and the noncollagenous proteins). The interactions between these components determine the nature of periodontal disease activity, whether gingivitis or periodontitis.

3.2.1 Polymorphonuclear leukocytes (PMNs/neutrophils)

PMNs are the first line of defense against bacteria, and proper PMN functionality is essential for protecting the integrity of the periodontium [14]. Neutrophils, present in clinically healthy gingival tissues, migrate through the intercellular spaces of the junctional epithelium into the sulcus [15, 16], in response to inflammatory chemotactic mediators such as IL-1, IL-8, or bacterial peptides (i.e., fMLP), and provide a "low-grade defense" against plaque bacteria [15, 17–19].

The proportion of neutrophils increases from 2% to 30% in modest inflammation causing vascular permeability which facilitates leukocyte emigration and increases the flow of GCF into the pocket [15]. At the molecular level, the interaction of adhesion molecules (e.g., ICAM-1) on endothelial and epithelial cells with β2 integrins on neutrophils facilitates neutrophil migration.

In the tissues, neutrophils phagocytose microorganisms and produce reactive oxygen species (ROS) to kill within the cells by the formation of neutrophil extracellular traps (NETs). NETs can be released by viable neutrophils and also following a form of programmed cell death called NETosis [20–24]. NETs are webs of complexed nuclear and mitochondrial chromatin/DNA and antimicrobial molecules such as histones and antimicrobial peptides (AMPs) [25, 26]. In established lesions, neutrophils release toxic superoxides, free oxygen radicals, and tissue degrading enzymes contributing to local inflammation and tissue damage [27].

3.2.2 Macrophages

Macrophages are mononuclear cells mainly participating in the early or innate defense against microorganisms and in specific immunity through their antigen-presenting function by releasing various cytokines. These cells present with varied phenotypes or subsets [28] and diverse functionality.

3.2.3 Natural killer cells

These killer cells are involved in the innate immune response by playing a vital role in host defenses against infected and malignant cells by producing cytokines such as TNF-α and interferon-g. These lymphocyte subgroup cells increase significantly from healthy human gingiva to diseased periodontal tissues [29, 30], in the immune response to plaque biofilm accumulation. Impaired lymphocyte function is also reported in various systemic conditions associated with periodontal diseases (e.g., Papillon-Lefèvre syndrome [31], Chédiak-Higashi syndrome [32], and smoking [33]).

3.2.4 Lymphocytes

Lymphocytes are one of the main types of immune cells with subsets T and B cells. When the innate or non-specific immunity is not able to cope with the

bacterial challenge, it activates the adaptive immune system by a group of cells, the T cells that have specific ability to present the bacterial antigens to the immune-competent cells. T lymphocytes mainly contributes to periodontal pathogenesis by direct involvement in periodontal bone resorption [34, 35]. B cells, the second major lymphocyte subset, give rise to plasma cells that produce specific antibodies when triggered by the antigen and other regulatory cells. The number of B cells increases from health to gingivitis to periodontitis [6, 36], and its major role is in the pathogenesis of periodontitis.

4. Immune responses in periodontal pathogenesis

The immune systems are essential for the maintenance of periodontal health and are mainly categorized as innate immune system and the adaptive immune system (**Figure 1**). It is now widely studied that immune responses are complex biologic networks in which pathogen recognition, innate immunity, and adaptive immunity are integrated and mutually dependent [37]. They are also integrated with other systems, including the nervous system, hematopoiesis, and homeostasis as well as elements of tissue repair and regeneration [38] as shown in **Figure 1**.

4.1 Innate immunity

The term "innate immunity" refers to the elements of the immune response that are determined by inherited factors, that have limited specificity, and do not change or improve during an immune response or as a result of previous exposure to a pathogen. Innate immune mechanisms include a number of relatively non-specific mechanisms, including the barrier effect of an intact epithelium, saliva, and GCF (**Figure 1**). The keratinized epithelium of the sulcular and gingival epithelial tissues provides protection for the underlying periodontal tissue in addition to acting as a barrier against bacteria and their products [15, 39]. Saliva, secreted from three major salivary glands, plays an important role in preventing the attachment of bacteria to the dentition and the oral mucosal surfaces. These components include molecules that non-specifically inhibit the formation of the plaque biofilm by inhibiting adherence to oral surfaces and promoting agglutination (e.g., mucins), those that inhibit specific virulence factors (e.g., histatins that neutralize lipopoly-saccharide (LPS)) and those that inhibit bacterial cell growth (e.g., lactoferrin) and

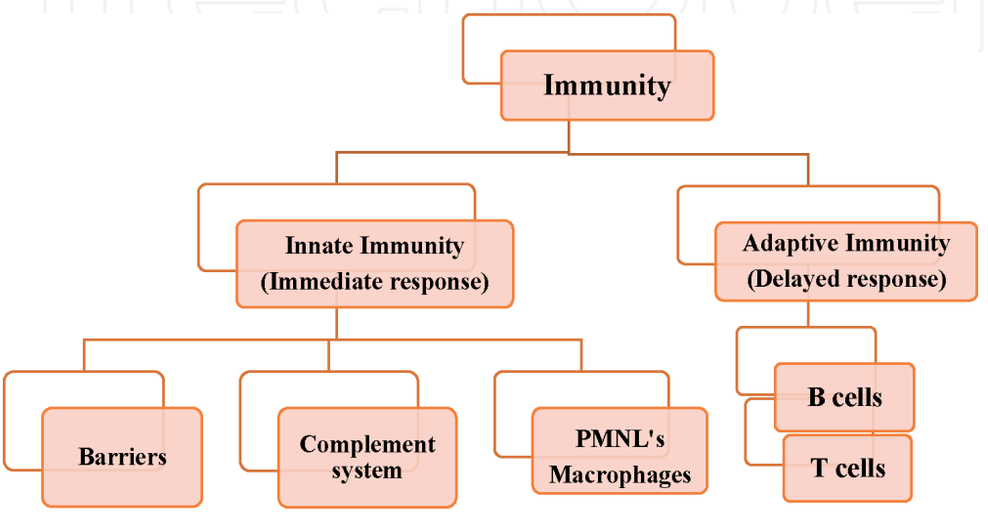

Figure 1.
Immune responses in periodontal pathogenesis.

that may induce cell death [40, 41]. GCF originating from the postcapillary venules of the gingival plexus carries blood components like neutrophils, antibodies, and complement components which help in host defense mechanism [42].

Saliva, as part of innate immune response, is a key factor in protecting dental enamel, gingiva, and mucosa by flushing microbes and foodstuffs, buffering acids, remineralizing the tooth, providing antimicrobial activity, and permitting selective adhesion of commensal microorganisms to maintain a symbiotic environment in the dental biofilm [43]. The salivary flow rate—high or low—is characteristic of each individual and [44–47] may promote salivary clearance of microbes from the oral cavity. Saliva also contains varying amounts of immunomodulatory interleukin-1β, interleukin-17, and interleukin-23, although it is not known whether they contribute to innate immunity on mucosal surfaces of the oral environment [48].

4.1.1 Pathogen recognition and activation of innate response

The recognition of pathogenic microorganisms and the recruitment of effector cells (e.g., neutrophils) and molecules (e.g., the complement system) are central to effective innate immunity. Innate immune responses are orchestrated by a broad range of cytokines, chemokines, and cell surface receptors, and the stimulation of innate immunity leads to a state of inflammation. When microbes penetrate the periodontal tissues, specialized cells of immune system, macrophages and dendritic cells, express a range of pattern recognition receptors (PRRs) which interact with specific molecular structures on microorganisms called microbe-associated molecular patterns (MAMPs) activating the innate immune responses (**Figure 2**).

4.2 Bacterial biofilm formation and development of a host response

Biofilms have been defined as "organized microbial communities characterized by a first group of colonizers being irreversibly adhered to a substrate or interphase in a wet media and the rest being embedded in a matrix composed of extracellular polysaccharides produced by the bacteria." The tooth surface provides a non-shedding hard surface where bacteria can adhere and form complex biofilms [8, 49].

The combination of natural host defense mechanisms and oral hygiene practices of individuals helps to have a balanced coexistence of oral microbiota in a healthy oral cavity which can be disturbed by either quantitative (higher bacterial load) or qualitative (growth of pathogenic species) changes in the biofilm leading to early stages of gingivitis [49].

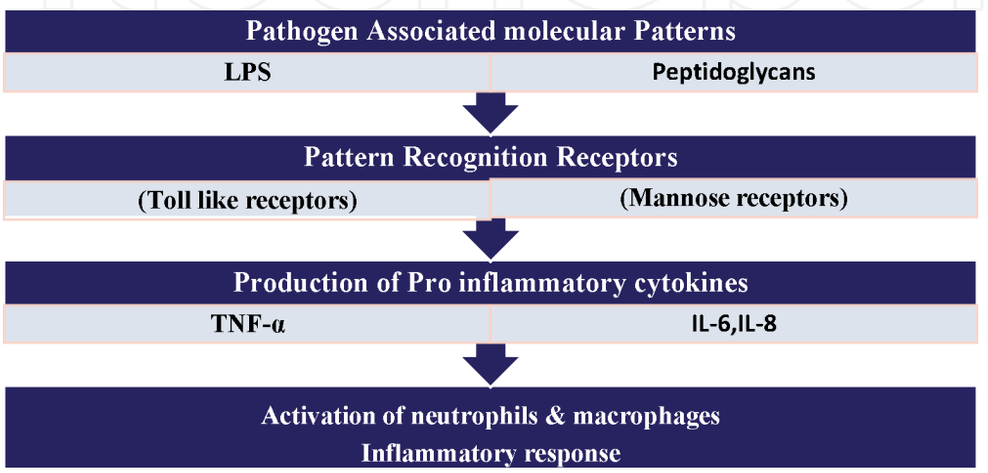

Figure 2.
Microbial- and host-associated pathogenesis of periodontal disease.

The epithelial attachment of tooth is a highly specialized structure where the junctional epithelial cells strongly attach to the tooth surface by a basal membrane, and hemidesmosomes providing the antibacterial defense mechanism by the high regeneration and desquamation rate and the continuous flow of gingival fluid through the gingival sulcus. The cells of the junctional epithelium with antibacterial proteins like human β-defensin 1 and chemokines along with intercellular adhesion molecule-1 (ICAM-1) and IL-8 help in the migration of PMN toward the gingival sulcus [8].

The protective function of the gingival epithelium is enhanced by keratinization, which helps resist abrasion. The gingival epithelium, as an innate immune barrier, is formed by interconnecting keratinocytes bridged one to another by cell adhesion molecules (CAMs) [50] which include integrins, mediating cell interactions with the extracellular matrix and basement membranes and contributing to cell-cell adhesion [51–53], as well as cadherins, which form tight contacts between cells [54]. The CAMs of the multilayered syncytium are susceptible to digestion by gingipains from *Porphyromonas gingivalis*, which could increase tissue permeability [55–58].

4.3 Innate immune response and gingivitis

Innate immunity is the first line of defense and the cells responsible for the innate immune response are mainly PMN, macrophages, and dendritic cells. Polymorphonuclear leukocytes (PMNs) are the first and predominant cells of the innate immune system in early gingivitis lesions [13].

The biofilm microbes on the tooth surfaces are recognized by the cells from the innate immunity through certain molecular patterns called pathogen-associated molecular patterns (PAMPs) which include lipopolysaccharide (LPS), peptidoglycans and lipoteichoic acids, N-formylmethionine, and lipoproteins. These molecules are recognized by pattern recognition receptors (PRRs) on the surface of PMNL and macrophages (**Figure 2**).

The two major families of PRRs that have been most extensively studied in the periodontium are the Toll-like receptor (TLRs) and the Nod-like receptors (NLRs) [59]. Toll-like receptors are unique receptors that recognize molecules that are broadly shared by microorganisms but are distinguishable from host molecules and can detect multiple pathogen-associated molecular patterns, including lipopolysaccharide, bacterial lipoproteins and lipoteichoic acids, flagellin, CpG DNA of bacteria and viruses, double-stranded RNA, and single-stranded viral RNA [60].

The TLR family currently consists of 10 known functional TLRs in humans [61, 62] in which TLR-1 through TLR-9 have been reported in the periodontium, in both health and disease [63]. When Toll-like receptors bind pathogen-associated molecular patterns, a series of intracellular events are initiated, leading to the production of cytokines, chemokines, and antimicrobial peptides (AMPs) [64]. Different Toll-like receptors induce different responses. For example, Toll-like receptors 1, 2, 4, 5, and 6 recognize products that are unique to bacteria and predominate in periodontal tissues, mainly in periodontitis [65] as shown in **Figure 2**.

4.4 Activation of adaptive immunity

If gingivitis persists without resolution, bacterial antigens are produced by lymphocytes, macrophages, and dendritic cells. Two different subgroups of lymphocytes, T lymphocytes and B lymphocytes, are released after being exposed with antigens by the innate immune cells. T cells are the effectors of cell-mediated immunity (delayed hypersensitivity), and B lymphocytes carry immunoglobulin molecules on their surface, which function as antigen receptors [66].

Adaptive immunity provides a more focused defense against infections than innate immune responses, which is slower and dependent on complex interactions between antigen-presenting cells (APCs) and T and B lymphocytes, specifically "cytotoxic T cells" and antibodies. Many histologic studies of periodontal disease [6, 67] have suggested the importance of adaptive immune responses in periodontal pathogenesis by the presence of leukocytes/neutrophils in the early stages of gingivitis and T cells in stable periodontal lesions. The T cells play a major role in maintaining tissue homeostasis against bacterial attack in plaque biofilm [68]. The transition from the established gingivitis lesion to periodontitis is mainly dominated by T and B cells.

5. Host-derived inflammatory mediators

The molecules participating in the cellular interactions are mainly categorized as proinflammatory and anti-inflammatory, and the balance between these two types of molecules determines the tissue response and the initiation or progression of disease. The key proinflammatory mediators in periodontal disease pathogenesis are as follows.

5.1 Cytokines

Cytokines are produced by resident cells, such as epithelial cells and fibroblasts, by phagocytes (neutrophils and macrophages) in the acute and early chronic phases of inflammation, and by immune cells (lymphocytes) in established and advanced lesions [69]. Interleukin-1β and interleukin-6 are the main innate cytokines and, together with tumor necrosis factor alpha, are the first to appear in the periodontal disease pathogenesis pathways [70]. Cytokines are effective in very low concentrations and have pleiotropic effects (i.e., multiple biologic activities) on a large number of cell types.

Cytokines are key inflammatory mediators in periodontal disease [71]. They are soluble proteins acting as messengers and binding to specific receptors on target cells to initiate intracellular signaling cascades resulting in cellular changes by altered gene regulation [72, 73]. The genetic regulation leading to the secretion of proinflammatory cytokines from a variety of cells is generally dependent on the activation of nuclear factor kappa-B transcription [74, 75]. The nuclear factor kappa-B-regulated pathways are activated by pathogen-associated molecular patterns, such as lipopolysaccharide, through the Toll-like receptor pathway [75].

5.1.1 Interleukin-1 family cytokines

The IL-1 family of cytokines comprises at least 11 members, including IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, and IL-33 [71].

IL-1α is an intracellular protein, produced by monocytic, epithelial, osteoblastic cells found in the extracellular environment or in the circulation [76]. Studies have reported elevated IL-1α levels in GCF and gingival tissues in patients with gingivitis and periodontitis [77] and involved in the bone loss that is associated with inflammation [78]. In recent nonhuman primate experiments, the use of a specific IL-1 inhibitor resulted in significant reduction of periodontopathogen-induced attachment loss, bone resorption, and inflammation [79] suggesting that IL-1 inhibitors might be useful in the management of periodontitis.

IL-1β produced by monocytes, macrophages, and neutrophils plays a key role in inflammation and immunity and along with lL-1α induces the synthesis and

secretion of other mediators that contribute to the inflammatory changes and tissue damage. IL-1β stimulates the synthesis of PGE2, platelet-activating factor, and nitrous oxide, resulting in vascular changes associated with inflammation [80]. Studies have shown increased concentration of IL-1β in GCF at sites affected by gingivitis [81] and tissue levels of IL-1β correlates with clinical periodontal disease severity [82]. IL-1β increases the expression of ICAM-1 on endothelial cells and stimulates the secretion of the chemokine CXCL8 (IL-8), thereby stimulating and facilitating the infiltration of neutrophils into the affected tissues [83]. Other members of IL family have more roles in the pathogenesis of periodontal disease.

5.1.2 Chemokines

Chemokines are chemotactic cytokines with an important role in the migration of phagocytic cells to the site of infection [84, 85]. Chemokines help in leukocyte recruitment in physiologic and pathologic conditions, which results in the chemotactic migration of neutrophils through the periodontal tissues toward the site of the bacterial challenge in the periodontal pocket [86].

Chemokines are synthesized by a variety of cells including endothelial, epithelial, and stromal cells, as well as leukocytes [87]. They are divided into two subfamilies: the CC subfamily and the CXC subfamily [88]. The chemokine CXCL8, also known as IL-8, has been found to be localized in the gingival tissues in areas of plaque biofilm accumulation and also in GCF112. Interaction between bacteria and keratinocytes results in the upregulation of IL-8 and ICAM-1 expression in the gingival epithelium, thereby stimulating neutrophil migration into the tissues and the gingival sulcus [89, 90].

Chemokines target leukocytes of the innate immune system, as well as lymphocytes of the adaptive immune system [91]. Chemokines play important roles in immune responses, repair, inflammation, and regulating osteoclast activity by influencing myeloid cell differentiation into osteoclasts, which may be of particular importance in the pathogenesis of periodontitis.

5.1.3 Tumor necrosis factor alpha

TNF-α is a molecularly distinct cytokine and a key inflammatory mediator in periodontal disease that shares many biologic activities with IL-1β [92]. Tumor necrosis factor alpha is a multi-effect cytokine that has many functions, from cell migration to tissue destruction. Tumor necrosis factor alpha impacts cell migration by inducing the upregulation of adhesion molecules and adhesion of neutrophils to the vessel wall, leading to extravasation. It also stimulates the production of chemokines involved in cell migration to infected and inflamed sites [93–96]. The proinflammatory effects of TNF-α include the stimulation of endothelial cells to express selectins that facilitate the leukocyte recruitment, the activation of macrophage IL-1β production, and the induction of PGE2 by macrophages and gingival fibroblasts [97].

5.2 Lipid mediators of inflammation-prostaglandins and thromboxanes

Prostaglandins are derived from the hydrolysis of membrane phospholipids. Prostaglandin E2 (PGE2) and thromboxane B2 are lipid molecules produced by many host cells through the cyclooxygenase pathway, one of the two major paths of arachidonic acid metabolism. Inflamed gingiva synthesizes significantly larger amounts of prostaglandins when incubated with arachidonic acid than in healthy gingiva [98]. Within gingival lesions, prostaglandin E2 is mainly localized to macrophage-like cells and is secreted when stimulated with bacterial lipopolysaccharide [99].

PGE2 induces the secretion of MMPs, as well as osteoclastic bone resorption, and it contributes significantly to the alveolar bone loss seen with all forms of periodontitis [100]. Prostaglandin E2 has biphasic actions on immune function. In high doses, it decreases the levels of IgG, but at low doses it has the potential to increase IgG. When combined with interleukin-4, low doses of prostaglandin E2 induce a synergistic rise in IgG production, suggesting an immune-regulatory role for prostaglandin E2 [101].

5.3 Matrix metalloproteinase

Matrix metalloproteinases are a family of structurally related, but genetically distinct, enzymes that degrade extracellular matrix and basement membrane components [102]. MMPs secreted by the majority of cell types in the periodontium, including fibroblasts, keratinocytes, endothelial cells, osteoclasts, neutrophils, and macrophages, are capable of degrading extracellular matrix molecules, including collagens [103, 104].

Most MMP activity in the periodontal tissues is derived from infiltrating inflammatory cells. In inflamed periodontal tissues, excessive quantities of MMPs are secreted by resident cells and neutrophils, resulting in the breakdown of the connective tissue matrix [105, 106] and leading to the development of collagen-depleted areas within the connective tissues. The predominant MMPs in periodontitis, MMP-8 and MMP-9, secreted by neutrophils [107] are effective in degrading type 1 collagen, which is the most abundant collagen type in the periodontal ligament [108].

Matrix metalloproteinase activity is controlled by changes in the delicate balance between the expression and synthesis of matrix metalloproteinases and their major endogenous inhibitors, tissue inhibitors of matrix metalloproteinases [102]. The prolonged and excessive release of large quantities of MMPs in the periodontium leads to the significant breakdown of structural components of the connective tissues, thereby contributing to the clinical signs of disease. In periodontal disease, secretion of specific matrix metalloproteinases is stimulated or downregulated by various cytokines. The main stimulatory cytokines for matrix metalloproteinases are tumor necrosis factor alpha, interleukin-1, and interleukin-6 [109].

6. Discussion

The immune and inflammatory processes that result from periodontal inflammation in response to bacterial biofilm are complex and mediated by a large number of proinflammatory and anti-inflammatory cytokines and enzymes that function as a network of mediators. Many studies have confirmed that immune cells from patients with periodontal disease secrete higher quantities of proinflammatory cytokines than do cells from persons who are periodontally healthy [72]. These findings led to the concept of the “hyperinflammatory” or “hyperresponsive” trait in which certain individuals possess a hyperinflammatory phenotype that accounts for their increased susceptibility to chronic inflammatory conditions such as periodontitis [110].

Although plaque bacteria initiate the inflammatory response, most of the tissue damage results from the host response, which is influenced by genetic factors, as well as environmental and acquired risk factors [111]. An essential goal of interventions in inflammatory disease is the return of tissue to homeostasis, by rapid elimination of invading leukocytes from a disease site [112].

Inadequate resolution of inflammation and failure to return tissue to homeostasis result in neutrophil-mediated destruction and chronic inflammation [113], with destruction of both extracellular matrix and bone [114] leading to advanced periodontitis.

Recently efforts are undergoing to control inflammation by the use of pharmacologic agents that inhibit proinflammatory mediator pathways (e.g., nonsteroidal anti-inflammatory drugs) [115] which target cyclooxygenase 1-dependent and cyclooxygenase 2-dependent pathways, inhibiting the generation of prostanoids. Accordingly, there is a need for the development of adjunctive agents for the management of periodontitis based on the current understanding of the etiology and pathobiology of periodontal disease. Host modulation therapy is an important emerging treatment strategy for managing all forms of periodontitis.

7. Conclusion

Periodontal diseases (gingivitis and periodontitis) are inflammatory diseases in which microbial etiologic factors induce a series of host responses that mediate inflammatory events. The maintenance of a healthy mucosal system is characterized by a continuous coordinated network of immune response that maintains the integrity of the tissue. Persistence of bacterial infection results in cellular and molecular modifications of the host response resulting in clinical manifestations of disease.

The presence of increased inflammation due to persistence of microbial pathogens with a failure of innate immunity systems will cause the shift of disease to a chronic state, later progressing to bone loss and periodontal tissue destruction. Even though persistent gingivitis is a risk factor for periodontal attachment loss, periodontitis is always a successor of gingivitis. However, studies in the last decade have brought significant understanding of the pathogenesis of periodontal disease by the recognition of dental plaque as a biofilm, discovery of new disease-associated bacterial species, the role of risk factors in disease susceptibility, and advanced host-derived cellular and molecular mechanisms in periodontal destruction.

Conflict of interest

None.

Notes/thanks/other declarations

Nil.

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