Periodontitis, the Current Cellular and Molecular Histopathologic Representation: A Narrative Review

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ABSTRACT

Periodontal disease is an inflammatory condition, clinically characterized by loss of periodontal attachment and bone loss around the tooth. This inflammatory process is initiated as a result of the pathogenic microbial insult which leads to an intense immunoinflammatory infiltrate in the periodontal tissue. This might lead to tooth loss if not appropriately managed. In gingivitis, a reversible form of periodontal disease that does not result in bone loss. Roy Page and Hubert Schroeder reported the first systematic model describing the host response in four types of histopathologic lesions: "initial," "early, "established" and "advanced". Although understanding of the periodontal pathogeneses in the development of gingivitis and periodontitis is largely based on the microbial involvement, further studies highlighted the complexity of the interactions between the periodontopathogens, host response, and modifying factors that contribute to the ultimate outcome of disease development and progression. The aim of this paper is to review the current aspects in the cellular and molecular pathogenesis of periodontal diseases.

Key words: Periodontitis, Pathogenesis, Immune, T-cells, NK-cells

INTRODUCTION

Periodontal diseases are the most common oral bacterial infection worldwide [1]. They occur as a result of a complex interaction between the periodontopathogens and host's inflammatory and immune system in addition to an interplay of environmental and genetic factors [2]. Periodontal diseases include gingivitis that is a reversible inflammation confined to the gingival tissues, and periodontitis, an irreversible and destructive form [3].

METHODOLOGY

The Pub-Med database of the US National Library of Medicine was searched using the keywords: "periodontal" and "pathogenesis". Google Scholar database was also searched for the additional literature search. The papers were manually selected after reading the abstracts and only relevant papers were included only if they were: (i) Written in English language, (ii) Published in the international peer-reviewed journals. Citation tracking was completed for included studies using Endnote™, version 9 (Clarivate Analytics, Boston, MA, USA).

The classic histopathologic characteristic of periodontal disease

The classical histopathologic 'road- map' of periodontal disease was described by Page et al. (Figure 1), based on assessment of tissues of naturally occurring and experimentally induced gingivitis and periodontitis in humans and animals and four lesions were reported. The initial, early and established lesions are recognized as distinctive stages of gingivitis, and the advanced lesion is distinguished as apparent periodontitis. In the initial lesion, the gingival tissues respond to inflammation within 2–4 days from plaque accumulation as an acute exudative vasculitis in the plexus of venules lateral to the junctional epithelium. In addition, polymorphonuclear leukocytes (PMNs) migrate

from the junctional epithelium to the gingival sulcus and the perivascular collagen is lost. Within 4–10 days, the early lesion develops and shows dense infiltrate of T lymphocytes and other mononuclear cells, and alteration in the gingival fibroblasts. The established lesion occurs within 2–3 weeks after plaque accumulation. It is dominated by B lymphocytes (plasma cells) and reveals more loss of gingival connective tissue matrix. A gradual gingival pocket is established during this stage but no bone loss is visible. Clinically, the established lesion demonstrates moderate to severe gingivitis which may progress to the advanced lesion. In the advanced lesion, the inflammatory infiltrate is composed of plasma cells and macrophages and it is associated with pocket formation and alveolar bone resorption [4-6].

Although understanding of the periodontal pathogeneses in the development of gingivitis and periodontitis is largely based on the microbial involvement, further studies highlighted the complexity of the interactions between the periodontopathogens, host response, and modifying factors that contribute to the ultimate outcome of disease development and progression [5,6].

Identifying the cellular and molecular hallmarks

Based on to the most well-established hypothesis of pathogenesis, host response plays a significant role in the complex etiology of periodontal disease [6]. In periodontitis, the host response is stimulated by the microbial challenges to initiate an inflammatory process as a defense mechanism. If not treated, the inflammation will progress to cause gingival connective tissue destruction and alveolar bone resorption. Environmental, habitual and genetic factors may change the pathways of the disease progression to either control the disease so the patient will be less susceptible to periodontitis or exacerbate the reaction making the patient more susceptible to periodontitis. This may explain the enormous differences in the patterns of destruction and patients' susceptibilities to periodontitis [7].

Pathogen virulence

Periodontal disease occurs when the equilibrium between the bacterial virulence and host's defense is disturbed resulting to a pathological response in the host's tissues [8]. The bacterial virulence can be classified into three categories; (i) Bacterial capability to adhere and colonize the area; (ii) Bacterial invasion to the connective tissue and; (iii) Interference with the host's defense mechanism.

Adhesion and colonization

The balance between the bacterial colonization and host's response determines the microbial homeostasis in the oral cavity. It starts at birth and continues throughout life [9,10]. If this balance is interrupted, the periodontopathogens will overcome the existing microbial homeostasis and cause pathology [11]. The gingival pocket provides an ideal environment for the anaerobic, motile, and low adherent periodontal pathogenic bacteria including *Prophromonas gingivalis (P. gingivalis), Tannerella forsythia (T. forsythia), Treponema denticola (T. denticola), Fusobacterium species, Prevotella species, Campylobacter species, and anaerobic streptococci* [12]. Furthermore, the gingival pocket offers the periodontal pathogenic bacteria a mechanical
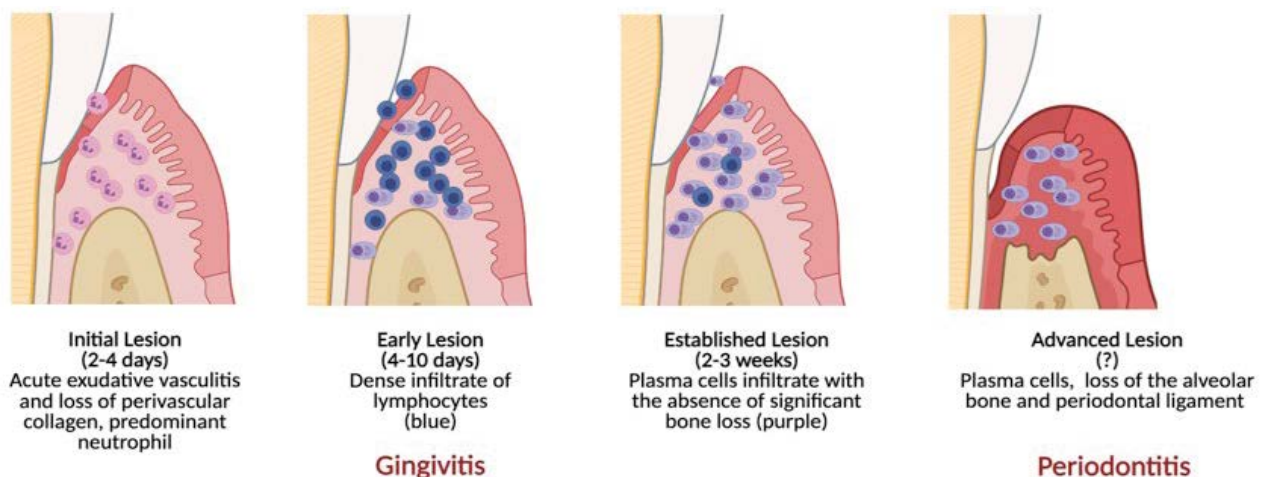

Figure 1: Periodontal disease pathogenesis as described by Page & Schroeder in 1976.

persistence and nutrients in the gingival exudate such as hemin, vitamins and hormones [11]. Concurrently, these bacteria produce numerous virulent factors that may interfere with the host's immune system such as proteolytic enzymes and endotoxins/lipopolysaccharides (LPS) and consequently they proliferate sub-gingivally to initiate and/or maintain inflammatory process [11,12].

Cell and tissue invasion

Bacterial invasion to the connective tissue is a critical event in the development of periodontitis [13,14]. It takes place if the junctional epithelium is disrupted with ulceration. Many acute infections had demonstrated bacterial invasion associated with neutrophil attraction. For example, in acute necrotizing ulcerative gingivitis, spirochetes are known to invade the connective tissues [15,16]. Periodontal abscess is also associated with bacterial invasion and growth into the tissues leading to fistula formation. In chronic periodontal disease, it is still controversial whether bacterial invasion takes place or not. However, it is confirmed that *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)* invade the underlying connective tissues in the aggressive form of periodontitis [14-17].

Bacterial invasion of periodontal tissues occurs through either intercellular or intracellular routes [14-18]. The interruption of the junctional epithelium allows motile bacteria such as Spirochetes, Treponema and Campylobacter species to penetrate the underlying connective tissues. On the other hand, some pathogenic bacteria such as *Treponema species and P. gingivalis* have the ability to produce specific gingipains (E-cadherin and occludin) that degrade proteins of the junctional epithelium [19]. The intracellular route attracts more attention as P. gingivalis T. forsythia, P. intermedia, and C. rectus were observed within the cells of periodontal tissue [20-22].

Evading and modulating of the host's response

The host reacts to the bacterial insult through inflammation and recruiting inflammatory mediators, neutrophils, macrophages, and antibodies [23]. In most cases, the neutrophils and macrophages can phagocytose the periodontal pathogenic bacteria. However, some bacteria have a specific ability to escape phagocytosis by producing leukotoxin or forming capsule and may result to spread of inflammation [24,25]. Leukotoxin is a well-known virulent factor produced by A. actinomycetemcomitans [26,27]. Furthermore, periodontopathogens can modulate the host immune response by producing endotoxins/lipopolysaccharides (LPS) that interact with B and T lymphocytes [28]. The toxicity of LPS varies greatly among various bacteria like *P. gingivalis* [29]. The outer membrane vesicles formed by P. gingivalis are mainly LPS membrane structures that contribute to P. gingivalis host interaction and pathogenicity [30].

T - Cells and periodontitis

When periodontitis is not resolved, a dense inflammatory infiltrate in the connective tissue activates the host immune response that is mainly mediated by the inflammatory cells such as neutrophils, monocytes/macrophages, and T and B lymphocytes [31]. T-lymphocytes are immune cells that are involved in the host defense and control immune-mediated inflammatory disease development. They can be distinguished from other lymphocytes by the presence of a T-cell receptor (TCR) on the cell surface. They are subdivided into Th, Treg, T-cytotoxic (CD8+), natural killer, and memory cells. In response to bacterial insult, antigen-presenting cells (APCs) will be activated and trigger the naive T-helper cells (Th0) to differentiate into T- cells subsets such as Th1, Th2, Th9, Th17, T-follicular helper (Tfh), and regulatory T-cells (Treg) based on their unique cytokine properties [31].

The role of T cells in periodontitis has been extensively revised by Campbell et al. The triggering of pro-inflammatory cytokines, such as IL-1β, IL-17E (IL-25) and IL-17 as a result of activation of Th1, Th2, Th17 and other immune cells such as dendritic cells, neutrophils, and B cells will result into expression of the receptor activator of nuclear factor kappa-B-ligand (RANKL) causing alveolar bone resorption [31].

The association of Th1 and Th2 with periodontal disease has been reported in the literature. A number of studies observed decreased levels of Th1 in the gingival crevicular fluid (GCF) [32], gingival mononuclear cells at periodontitis sites [33] and peripheral blood mononuclear cells in patients with periodontitis cocultured with *P. gingivalis and F. nucleatum* [34]. However,

increased Th2 responses in periodontitis patients have been detected in gingival tissues [35,36], extracted gingival mononuclear cells [37] and GCF [38]. In addition, both Th1 and Th2 cytokines have been observed in experimental studies of cells extracted from the periodontal lesions [39,40] and IL-1β, TNF-α, and IL-17 were highly expressed in patients with periodontitis [41].

T cells have a critical role in the secretion of IL-17 which is associated with alveolar bone loss. In patients with chronic periodontitis, levels of IFN-γ, IL-17A, and T-bet mRNA were significantly higher than healthy controls [42]. This might suggest that Th1 and Th17 cells play a significant role in the pathogenesis of chronic periodontitis. The major source of IL-17 is CD4+ T cells, which increased significantly in periodontitis patients [43,44]. Furthermore, Th17 cells in the presence of periodontitis are dependent on the local pathogenic bacteria, and both IL-6 and IL-23 are needed for their accumulation [45]. Thus, the immunoregulatory control of T cells and their effector cytokines is fundamental in defining the ultimate outcome of chronic periodontitis.

Natural killer cells and periodontitis

Natural Killer cells (NK cells) are discrete cytotoxic lineage of lymphocytes which play an important role in the pathobiology of periodontitis. NK cells are one of the major components of the innate immune system. They play a regulatory function by secreting cytokines and gamma interferon (IFN-γ) [46,47]. NK cells are activated by CD2-like receptors which were reported to activate cytotoxic cells which in turn activate CD8 in T and B cells [48-50]. This activation process might be involved in periodontal tissue destruction [50-52]. Furthermore, production of IFN-γ by NK cells has been observed to occur when dendritic cells (DCs) were cocultured with periodontopathogens such as *P. gingivalis* and *A. actinomycetemcomitans* [53,54]. Moreover, F. nucleatum can activate receptor NKp46 in NK cells leading to periodontal bone loss [55]. Recently, Gaudilliere and his coworkers [56] observed exaggerated proinflammatory responses to P. gingivalis–derived lipopolysaccharides in the circulating neutrophils and monocytes of patients with chronic periodontitis compared to healthy controls. This immune alteration was not detectable three weeks after periodontal treatment. Although, the role of NK cells in periodontal disease is well established, the mechanisms underlying their activation during periodontal disease are not fully understood [57].

CONCLUSION

Although the proposed model is reasonable, our understanding of how inflammatory host response is regulated is far from complete. New discoveries are needed to enhance the information obtained from the currently available indicators and understand the disease mechanisms. As a result, there is a great increase in the interest to apply emerging technologies in order to improve the understanding of the disease processes and the underlaying factors.

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