Introduction

The understanding of the etiology and pathogenesis of periodontal disease has changed significantly in the last five decades, not only with regards to the specific microorganisms associated with the onset and progression of the disease, but also the dramatically elevated emphasis on the primary role of the host response in the destruction of the periodontal tissues. In this regard, Van Dyke (2014) recently highlighted the concept that the host-response in periodontal disease may not only be induced by (or follow) the microbiological insult to the gingival/periodontal tissues (traditional view), but may also precede, or result in, the development of a recognizable pathogenic microbial biofilm; this concept addresses the recent controversy as to whether chronic periodontitis should be categorized as an “infectious” disease (traditional view) or, that chronic periodontitis is an “inflammatory” disease [1].

Etiology

By the mid-1960s, the concept took hold that the initiation and progression of periodontal disease is caused by the supra and subgingival dental plaque which is now called the microbial biofilm. At that time, a key series of longitudinal clinical studies were carried out by Dr. Harald Loe and his colleagues collectively called the “Experimental Gingivitis in Man.” The aim of these experiments on human subjects was to determine whether or not there is a cause-effect relationship between dental plaque accumulation and the onset of gingival inflammation. The initial experiment was performed on 12 dental students who exhibited good oral hygiene and gingival health. Before beginning this study, the subjects were administered repeated dental prophylaxis and oral hygiene instruction so that their Plaque Index (PI) and Gingival Index (GI) were essentially zero, ie., no detectable plaque adherent to their teeth and no clinically-evident gingival inflammation. Each subject was then instructed not to brush their teeth for a period of time. Immediately, the mean PI increased and days later the mean GI increased. They concluded that accumulation of dental plaque (now called the microbial biofilm) is the cause of the onset of gingivitis. Moreover, when the subjects were told to begin brushing their teeth again, the mean PI immediately decreased, and days later the mean GI decreased back to the normal levels seen prior to initiating this longitudinal protocol [2]. Additional studies on human subjects by this group identified the shift of the plaque microflora from a predominantly aerobic Gram-positive biofilm, associated with gingival health, to a biofilm which consisted primarily of anaerobic Gram-negative microorganisms [3, 4]; the identification and characterization of these “periodontal pathogens” has been a major “driver” of periodontal research for the past 5 decades (see below). Soon afterward Lindheand his colleagues (1973) extended Löe’s observations by showing that allowing dental plaque to accumulate in the beagle dog model was followed, in time, by a rise in the gingival crevicular fluid flow, then an increase in gingival inflammation which was assessed clinically and then months later, by increased pocket depth indicating the development of tissue breakdown and the conversion of gingivitis to periodontitis [5].

More recently the focus on the etiology of peridontal disease has changed markedly with a focus on specific anaerobic microorganisms as the initiating factor. A number of specific bacteria, such as porphyromonas gingivalis (P. gingivalis), Tanneralla forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans (previously known as Actinobacillus actinomyce-
temcomitans), prevotella intermedia, and others including Fusobacterium nucleatum, Wolinella recta, and spirochetes, have been associated with severe forms of periodontal disease [6]. Even today, the predominant view highlights the so-called “red complex” (which includes P. gingivalis, Tannerella forsythia, Treponema denticola) as the primary etiologic factor in the most common periodontal disease (excluding gingivitis) chronic periodontitis [7], although in more aggressive (and rare) forms of...
periodontal disease, localized and generalized aggressive periodontitis, other microorganisms have been highlighted, i.e., *Aggregatibacter actinomycetemcomitans* [8, 9]. Furthermore, a group of pathogens not typically present in the oral cavity has also been linked to periodontal disease, such as *Enterobacteracea*, *Pseudomonadacea*, and *Acinetobacter* [10]. Periodontitis is a chronic inflammatory disease, in which severe forms of the disease are associated with specific bacteria that have colonized the subgingival area regardless of the host’s protective mechanisms; as discussed below, the response of the host to the microbial irritants [e.g., endotoxin/lipopolysaccharide (LPS)] is now recognized to be essentially responsible for the connective tissue breakdown and loss of alveolar bone which are the essential characteristics of this disease. Nevertheless, the vulnerability of individuals seems to vary greatly depending on which risk factors are functioning [11]. Moreover, as recently reiterated by Van Dyke (2014), this association between these specific Gram-negative microorganisms and the onset and progression of periodontitis may reflect, at least in part, the inflammation-altered-environment in the periodontal lesion (periodontal pocket) causing the normal Gram-positive microflora to shift to a more anaerobic Gram-negative microbial biofilm associated with disease [1].

**Pathogenesis: Germ-Free Models and Periodontitis Pathogenic Mechanisms--Early Studies**

In the early 1960s, a major breakthrough was achieved by Dr. Jerome Gross at Harvard medical school when he discovered, for the first time ever, a proteolytic enzyme produced by animal tissues (the "host") that could degrade the triple helical collagen molecule under physiologic condition of pH and temperature; he called this enzyme, animal collagenase. Until this landmark discovery, it was widely thought that the triple helix collagen molecule, which is the major constituent of all connective tissues in the body, was not susceptible to the then-known neutral proteinases such as trypsin, plasmin, neutrophil elastase, etc. This breakthrough experiment was published in 1962 [12]. Soon afterwards, another major observation regarding collagen destruction was made by a dental researcher at NIDCR/NIH, Dr. Harold Fullmer. He used the sterile J. Gross tissue-culture system, and a collagen matrix comprised of triple-helical collagen molecules, and found that human gingiva, surgically excised from a healthy site, did not produce a zone of lysis of a collagen gel in tissue culture whereas gingiva excised from a diseased site (i.e., a deep pocket) produced a dramatic increase in mammalian collagenase as made evident by the zone of lysis in tissue culture, and the production of 3/4 and 1/4 split products of collagen characteristically produced by host or mammalian collagenase [13]. A few years later, Ivanji and his colleagues in Britain (1972), described the role of the immune response in periodontal destruction independent of bacteria. Their data suggested that cell-mediated immunity plays a significant role in the pathogenesis of periodontal disease [14]. Subsequently, Taubman et al. (1984) determined the role of the immune response in a germ-free rat model of experimental periodontal disease. His experiments supported the idea that T-cell functions and regulation of the immune response by the thymus can have protective and/or destructive effects in periodontal disease. He concluded that in order to control this disease, it would be crucial to enhance the protective "arm" of the immune response, and suppress its destructive aspect [15].

About the same time it was becoming increasingly clear that systemic diseases particularly diabetes can increase the severity of periodontal disease in both human and experimental animals [16]. In earlier experiments, Golub et al. (1973) addressed the mechanisms by which diabetes can increase periodontal breakdown. Using the tissue culture technique of [12, 13], he and his colleagues showed, for the first time in any tissue, that inducing experimental diabetes (alloxan or streptozotocin injection) and severe hyperglycemia dramatically increased mammalian or host derived collagenase activity; note that the tissues he cultured in the collagenolytic system were gingival. He demonstrated that the viable gingiva in tissue culture, under sterile conditions, when derived from hyperglycemic diabetic rats produced more solubilization and degradation of radioactive collagen fibers than gingiva from non-diabetic rats and that reducing blood glucose levels by treating the diabetes with insulin injections reduced the excess gingival collagenase activity. This demonstrated that diabetes increases mammalian collagenase activity as a mechanism for pathologic periodontal tissue breakdown and, assuming the same effect could be found in other tissues as well, could also provide a mechanism which mediates a variety of complications throughout the body (in fact, in recent years, diabetes has been found to increase MMPs systemically, not just locally in the gingiva; [17–19]).

As reviewed extensively by Golub et al. (1998), the next question asked was: did diabetes and hyperglycemia result in pathologically excessive mammalian (host-derived) collagenase activity in the gingiva (a) by creating an environment in the gingival crevice (e.g., elevated glucose and urea concentrations; hypoxia, etc…) favoring the overgrowth of an anaerobic Gram-negative microflora which resulted in elevated levels of endotoxin penetrating the gingival tissues, or (b) by mechanisms independent of a microbial shift and only dependent on an altered host response (a dominant pathway suggested was the long-term hyperglycemia producing AGE/RAGE interaction to up-regulate MMP production;[18, 20]. In the microbially-induced pathway, diabetes was thought to alter the microbial biofilm by increasing the level of Gram-negative anaerobic bacteria in the periodontal pocket. This would result in elevated endotoxin (LPS) levels in the gingival pocket, and then the endotoxin could penetrate the diabetes-damaged gingival crevicular epithelium to stimulate the host cells to produce elevated collagenase and other MMPs which would degrade collagen and the other connective tissue constituents. In the alternative pathway (host-mediated pathway), the view was that diabetes increases gingival collagenase independent of bacteria. For example, hyperglycemia would produce advanced glycation end products (AGEs) which would then react with RAGEs on the surface...
of host cells such as, fibroblast and macrophages which would stimulate MMP production. To identify which hypothetical pathway was correct, Golub and his group (1983) decided to suppress the microbial pathway by treating the diabetics with minocycline (a tetracycline antibiotic) to see if suppressing the bacterial pathway cancels the diabetic effect on gingival collagenase. At first glance it appeared that the excess collagenase in the diabetic gingiva was due to an overgrowth of periodontal bacteria, because this effect was inhibited by treating the diabetic rats with the antibiotic minocycline. However, to ensure that the tetracycline was not acting by some unknown non-antimicrobial mechanism, the same experiment was repeated using a germ-free rat model and, surprisingly, the effect of the drug was virtually the same. Once again diabetes, even in the germ-free rats, dramatically increased mammalian collagenase activity, meaning that the shift in microbial effect was not related to the excess collagenase activity in the gingiva of diabetics. Even more intriguing, treating the germ-free diabetic rats with this tetracycline again reduced the excess mammalian collagenase activity to near-normal levels. This demonstrated, for the first time ever, that tetracyclines could inhibit host-derived MMPs and inhibit collagen degradation, and by mechanisms unrelated to the antibiotic activity of TCs. Ultimately, this discovery resulted in the development of several non-antibiotic formulations of tetracyclines for the treatment of a variety of collagen destructive diseases [20-23]. Moreover, this novel non-antibiotic property of tetracyclines has been confirmed by various researchers internationally [24-26].

**Immunopathogenesis of Periodontal Disease—recent studies**

It has been accepted traditionally that periodontal disease is induced by bacteria in dental plaque or biofilm; moreover, evidence now exists that specific microorganisms may be responsible for more aggressive forms of the disease. However, it has also been acknowledged that, some individuals can harbor these specific bacteria, and NOT show signs of disease progression [27]. Host factors related to disease susceptibility is of extreme importance to the outcome of periodontal disease, and even though periodontal pathogens are still regarded as the main initiating agents, the host's immune-inflammatory response to these pathogens plays an essential role [28]. In fact, a recent essay by Van Dyke (2014) recommended that chronic periodontitis should no longer be classified as an "infectious" disease, and should now be considered (like rheumatoid arthritis, inflammatory bowel disease/Crohn's disease, psoriasis) an "immune-inflammatory" disease.

Inflammation in the periodontal tissues is regulated by the expression of mediators generated by the host that cause a number of pleiotropic events resulting in the recruitment of inflammatory cells and elaboration of biologic mediators by leukocytes and macrophages, and other cells e.g., fibroblast, epithelial cells, and bone cells. If the inflammation is temporary or acute in nature, it can protect the host by stimulating defense mechanisms combating infection and initiating wound healing. On the other hand, if the inflammation is severe and prolonged (or unresolved), it can cause substantial tissue breakdown [29]. Many cell types and mediators, including T helper 1 and T helper 2 lymphocytes, cytokines and chemokines, seem to participate in the immunopathogenesis of periodontal diseases [30]. Chronic inflammatory periodontal disease manifests itself clinically, as at least two distinct diseases. Data, based on microbiological, immunological and animal studies, have revealed that some types of periodontal disease in adults can stay "silent" or non-progressive for many years and do not jeopardize the life of the dentition (i.e., gingivitis), while other types, regardless of extensive treatment, continue to progress and, eventually, can cause tooth loss (i.e., periodontitis). Even though periodontal bacteria are the initiating agents in periodontitis, subsequent progression and severity of the disease are thought to be determined by the host immune response [31]. Similar to other chronic inflammatory diseases, a complex network of cytokines take part as vital mediators in controlling cellular interactions. As observed in many clinical and experimental studies, LPS and other products of bacteria can stimulate the host cells to release pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and others. Target cells in turn are stimulated to elaborate still other cytokines (some anti-inflammatory, e.g., IL-10), inflammatory mediators and, in the case of tissue destructive diseases, catabolic enzymes. The cytokine network controls the inflammatory mechanisms to either intensify or restrain tissue reactions [32]. As a result of the site-specific nature of the periodontal disease process, this network has to be securely controlled by local processes. The initial (acute) inflammatory phase includes a reactive and defensive response to the bacterial products. Increased neutrophil migration into the sulcus, increased flow of serum proteins into the tissues, proliferation of epithelial cells, and subsequent local accumulation of mononuclear cells accentuates these phenomena [32]. The innate immune system in the periodontal microenvironment consists of multiple cell types, including epithelial cells, CD38+ Langerhans cells in oral mucosa, tissue macrophages, neutrophils, and dendritic cells [33]. Their role in the periodontium is to provide defense against the invasion of pathogens and the maintenance of tissue integrity. This innate immune system is effective in protecting the periodontium as evidenced by the limited number of bacteria actually invading the periodontal tissues and the very rare occurrence of sepsis in spite of the long-term bacterial load in the dental biofilm associated with periodontal disease. However, even though most of the microorganisms are located outside the periodontal tissues, their microbial associated molecular patterns (MAMPs) trigger innate immune responses by activating Toll-like receptor (TLR) signaling which, in turn, may initiate and modulate adaptive immune responses [34]. These receptors are expressed by immune cells such as macrophages, neutrophils, and dendritic cells as well as by non-immune resident cells, such as fibroblasts and epithelial cells. Within the periodontal tissues, TLR2 and TLR4 expression are increased in severe periodontitis, suggesting that these receptors have an increased capacity to signal and influence downstream cytokine expression [35, 36].
Regarding the role of the biofilm, their metabolic products, notably LPS/endotoxin component of the cell wall of Gram-negative pathogens, is one of the main microbial associated molecular patterns that can stimulate the expression and production of pro-inflammatory cytokines through activation of TLRs. These cytokines e.g., IL-1β, TNF-α, and IL-6 are considered to be the essential initiators involved in the destruction of soft and hard tissues that are the hallmarks of aggressive periodontal disease. This important role of LPS for periodontal diseases is demonstrated in the LPS-model of experimentally induced periodontal disease, where direct injection of LPS into the gingival tissues initiates a local host response that involves recruitment of inflammatory cells, generation of prostanoids and cytokines, secretion of lytic enzymes and stimulation of osteoclasts, culminating in the destruction of both soft and mineralized tissues of the periodontium [37]. Virtually the same host response can be achieved by infecting gnotobiotic rats with a periopathogen such as P. gingivalis [38].

IL-1 and TNF-α can up-regulate collagenases and PGE2 synthesis which mediate breakdown of periodontal tissues. In acute gingivitis, T cells dominate, whereas in the later-occurring immune response, large numbers of B cells predominate. This has led to debates on the defensive role of cellular immune responses in gingivitis. Chronic inflammation is thought to be controlled mainly by IL-2, IFN-γ, IL-10, and IL-12, while acute inflammation is generated mainly by elevated levels of IL-1 family of cytokines, as well as TNF-α. In this regard, it should be recognized that the most common type of periodontitis, chronic periodontitis, is actually characterized by a period of disease activity characterized by infiltration of acute inflammatory cells the polymorphonuclear leukocytes (PMNL) which migrate into the periodontal pocket while chronic inflammatory cells remain in the periodontal connective tissue. Therefore, chronic periodontitis is characterized by “bursts” of acute inflammation and tissue destruction (exacerbation) followed by periods of remission. Moreover, changes in expression of entire cytokine families might be consistent with the concept of a change from a T helper 1 to T helper 2 responses. This change has been noticed in chronic diseases and is implicated in chronic periodontal inflammation. Furthermore, the experimental reduction of neutrophilic granulocytes in the dento-gingival area leads to enhanced subgingival microbial colonization even in the presence of mechanical elimination of supragingival plaque [32].

Periodontal disease is a peripheral infection mediated by a variety of Gram-negative bacteria. T-lymphocytes that can be present in the dense inflammatory infiltrate in this disease. CD4+ and CD8+ T-cells are found in periodontal lesions, as memory/activated T-lymphocytes. Th1-type T-cells upregulate the production of pro-inflammatory cytokines IL-1 and TNF-α, which can cause resorption of bone by promoting the differentiation of osteoclast precursors and subsequent osteoclast activation. Such osteoclast differentiation is reliant on activation of osteoprotegerin ligand (OPG-L) production by osteoblasts. The tumor necrosis factor (TNF) family of molecules, the receptor activator for NF-kB ligand (RANKL), its receptor RANK, and the natural antagonists, osteoprotegerin (OPG), have all been found to be key modulators of bone remodeling and are directly involved in the differentiation, stimulation, and survival of osteoclasts and osteoclast precursors [39]. Activated CD4+ T cells express RANKL, which can directly activate osteoclastogenesis and the loss of alveolar bone which characterizes periodontitis [39].

In contrast, stimulated T-cells, as a result of direct production and expression of OPG-L, can stimulate the differentiation of osteoclasts directly. OPG-L seems to be mostly expressed on Th1-type cells. The contribution of T-cell in periodontal bone resorption seems to be reliant on the degree of Th 1-type T-cell recruitment into inflamed gingival tissues. This T-cell recruitment is mediated by adhesion molecules and chemokines/chemokine receptors. The T-cell characteristics in inflamed periodontal tissues can be compared with those in rheumatoid arthritis, in which bone resorption is often attributed to Th1-type T-cell involvement [39].

**Link between Local Chronic Periodontitis and Systemic circulation**

Goncalves et al. (2010) reported that peripheral blood mononuclear cell (PBMC) from patients with generalized chronic periodontitis and no history of systemic diseases released increased levels of TNF-α and IL-6 in cell culture compared to healthy subjects without chronic periodontitis. The increased production of such pro-inflammatory cytokines indicates a hyper-reactivity of PBMC from patients with local periodontitis and periodontal tissue destruction plus a systemic inflammatory burden [40]. However, the concept that periodontal disease increases the levels of TNF-α and IL-6 in the circulation of patients remains controversial [41, 42]. Some studies have found higher plasma levels of TNF-α and IL-6 in subjects with periodontitis, compared to healthy controls, which are reduced after periodontal therapy, while others have not found this association [43, 44].

Another study involving PBMC also demonstrated that LPS-stimulated monocytes control subjects [45]. Gustafsson et al. (2006) also showed a tendency for a higher release of TNF-α by stimulated mononuclear cells from subjects with treated periodontitis when compared to healthy ones [46]. On the other hand, Fokkema et al. (2002) found no differences in the release of TNF-α and IL-6 in the E. coli LPS-stimulated whole blood cell cultures (WBCC) comparing periodontitis and healthy subjects [47]. These contradictory results can be explained, in part, by methodological and population differences including the inclusion of smokers, ethnic characteristics of the populations, sample size, types (chronic or aggressive) and severity of periodontitis, type of cell culture (WBCC or PBMC), duration and methods of cell stimulation and differences in assays for these inflammatory cytokines.

Similar differences in study results have been found using other types of leukocytes and other cytokines. As examples, Fokkema et al. (2002) demonstrated that the levels of IL-8 in the supernatants of LPS-stimulated WBCC from patients with periodontitis were higher than those from...
controls [47]. Other studies also demonstrated that the plasma levels of IL-8 were higher in patients with periodontitis than in healthy individuals [44]. On the other hand, Restaino et al. (2007) showed that IL-8 secretion promoted by various stimulating agents in WBCC did not differ between periodontitis and control groups [48]. Interestingly, the authors noticed that, unlike the control group, the levels of IL-8 secreted by stimulated neutrophils from periodontitis subjects were significantly lower than those from periodontally healthy individuals. However, methodological differences between these various studies have hindered any direct comparisons [48].

Goncalves et al. (2010) found no differences between periodontitis and healthy groups with regard to the levels of the anti-inflammatory cytokine, IL-10, indicating that LPS-stimulated PBMC of periodontitis and non-periodontitis subjects may present a similar ability to produce this regulatory anti-inflammatory cytokine [40]. These findings are supported by a previous study using the supernatants of stimulated WBCC from chronic periodontitis subjects [47]. In relation to the plasma levels of IL-10, Monteiro et al. (2009) did not find differences in the concentration of IL-10 between chronic periodontitis and healthy subjects [44]. On the other hand, Havemose-Poulsen et al. (2005) observed higher plasma levels of IL-10 in generalized aggressive periodontitis individuals, when compared to healthy ones [49].

Increased levels of circulating monocytes have been observed in subjects with periodontitis [47]. Gustafsson et al. (2006) demonstrated that mononuclear cells and neutrophils from subjects with treated periodontitis and slight periodontal inflammation are also hyper-reactive and susceptible to relapse of the disease when compared to periodontally healthy subjects [46]. In addition, data on whether periodontal therapy affects the serum levels of CRP and other systemic biomarkers are still inconclusive [48]. Therefore, it is reasonable to suggest that subjects with periodontitis may have a constitutionally different host response in PMBCs, independent of the presence of active disease. However, it could also be argued that patients with periodontitis, as a result of this common oral inflammatory disease, develop systemic inflammation including elevated levels of cytokines and acute phase protein, e.g., CRP. From these findings, it may also be speculated that high reactivity of immune cells to LPS may be a susceptibility factor for both periodontal tissue breakdown and systemic diseases in individuals with periodontitis.

Regulatory Pathways in Chronic Periodontitis

Activation of NF-kB is known to be essential for the expression of inflammatory cytokines involved in the pathogenesis of various inflammatory diseases [50, 51], suggesting that this cell signaling pathway could be a major target for host modulation therapies. Activation of NF-kB was also seen in oral epithelial cells exposed to the periodontal pathogens, fusobacterium nucleatum and P. gingivalis [52], indicating the crucial role of NF-kB on innate immunity in the oral cavity. In this regard, stimulation of gene expression in human mononcytic cell line by P. gingivalis LPS was abolished by inactivation of NF-kB [53]. In another study, inhibition of NF-kB activation by endocannabinoids (derived from arachidonic acids), which are lipid mediators with immunosuppressive and anti-inflammatory properties, decreased the production of pro-inflammatory mediators (IL-6, IL-8 and MCP-1) induced by P. gingivalis LPS in human gingival fibroblasts, another resident cell type with an important role in innate immune response in periodontal diseases. All of these (and other) studies indicate the role of NF-kB in the expression of fundamental mediators in periodontal disease [54].

Discussion

Historically, and still today, treatment of chronic periodontitis has overwhelmingly focused on reducing the bacterial “burden” in the periodontal pocket and reduction of periodontopathogens e.g., P. gingivalis. Traditionally, this has included mechanical debridement procedures such as scaling and root planing (SRP) and surgical reduction of pocket depth to reduce the bacterial “load” in the periodontal lesion, and enhancing the effectiveness of plaque removal by optimizing oral hygiene procedures. Both topically applied (e.g., aridox; arestin; periochip) and systemic (e.g., metronidazole, azithromycin) antimicrobials/antibiotics as adjunctive therapy have also been advocated [55] although a recent comprehensive statistical (retrospective cohort) study did not find any benefit of adjunctive systemic antibiotic therapy in the management of the periodontal patient based on the ultimate outcome/morbidity of chronic periodontitis, i.e., tooth loss in adult patients [56]. Also, of course, the excessive use of antibiotics, resulting in the emergence of antibiotic-resistant bacteria, must be considered a serious detrimental consequence. In this regard, a number of years ago Golub and his group [20-22] introduced and developed NON-antibiotic formulations of the common antibiotic, the tetracyclines, as host-modulating drugs (based on mechanisms of action previously unrecognized in the medical and dental fields) in the management of chronic periodontitis and various relevant medical disorders, and this has been thoroughly reviewed [20, 22, 23, 57].

Extracellular matrix (ECM) breakdown, during different periodontal diseases, is mediated by a complex cascade including host-derived proteinases [3]. The significance of the host inflammatory response in periodontal disease presents an opportunity to explore novel approaches for treating periodontitis involving the targeting of the host response. Host modulatory therapy (HMT), first introduced both by Williams using non-steroidal anti-inflammatory drugs or NSAIDs [58-61] and by Golub using non-antimicrobial tetracyclines as MMP-inhibitors; [11-13]; was designed to be adjunctive to the use of conventional periodontal treatments, primarily (but not only) scaling and root planing, that reduce the bacterial “load” in the periodontal pocket. HMT was developed to treat the host inflammatory and collagenolytic responses in periodontal pathogenesis, and functions by inhibiting the activity and/or down-regulating the expression of MMPs, such as the collagenases and

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gelatinases, as well as suppressing cytokines, such as IL-1β, IL-6, and TNF-α, and other mediators of inflammation and connective tissue destruction including the “normalization” of excessive osteoclast-mediated bone resorption [3,4,14]. More recently, a combination of two different host-modulatory treatments (SDD and low-dose flurbiprofen) was combined in a clinical trial on periodontal patients requiring surgical treatment and did show a synergistic response in modulating host mediators (MMPs and neutrophil elastase) in the excised gingival tissues [15]. Ever since the mid-1960’s-1970’s, with the recognition that the host response is primarily the propagating factor in periodontitis and bone destruction [13, 66], the concept of HMT, and its development, has evolved progressively. Several additional approaches, beyond those described above, have also been advocated including the use of bisphosphonates, resveratrol, and, most recently, the resolvins based on omega-3 fatty acids [67]. However, with the earlier discovery of the unexpected ability of the tetracycline (TC) family of antibiotics (e.g., minocycline, doxycycline) to block host-derived MMPs plus other anti-inflammatory effects of these drugs [13], and the development of non-antimicrobial formulations of doxycycline as MMP inhibitors [5, 19], only this HMT strategy has been FDA-approved and ADA-recommended as a safe and effective adjunct to non-surgical periodontal therapy. Therefore, the effective long-term management of periodontitis needs a treatment strategy that address both etiologic elements. The role of MMPs, cytokines, and other mediators within the process of periodontitis distinguishes them as viable targets for a chemotherapeutic approach. Host modulation as adjunctive therapies to boost the efficacy of mechanical debridement will contribute favorably to a combined approach for the management of periodontitis.

References


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