frontiers | Frontiers in Dental Medicine

REVIEW
published: 13 May 2022
doi: 10.3389/fdmed.2022.879131

Modulating the Immune Response in Periodontitis

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Periodontitis is a chronic inflammatory condition initiated by the accumulation of bacterial biofilm. It is highly prevalent and when left untreated can lead to tooth loss. The presence of bacterial biofilm is essential for the initiation of the inflammatory response but is not the sole initiator. Currently it is unknown which mechanisms drive the dysbiosis of the bacterial biofilm leading to the dysregulation of the inflammatory response. Other players in this equation include environmental, systemic, and genetic factors which can play a role in exacerbating the inflammatory response. Treatment of periodontal disease consists of removal of the bacterial biofilm with the goal of resolving the inflammatory response; however, this does not occur in every case. Understanding the way the inflammatory response does not return to a state of homeostasis has led investigators to consider both systemic and local pharmacological interventions. Nonetheless, a better understanding of the impact that genetics and environmental factors may have on the inflammatory response could be key to helping identify how inflammation can be modulated therefore stopping the destruction of the periodontium. In this article, we will explore the current evidence associating the microbial dysbiosis and the dysregulation of the immune response, potential mechanisms or pathways that may be targeted for the modulation of the inflammatory response, and discuss the advantages and drawbacks associated with local and systemic inflammatory modulation in the management of periodontal disease. This information will be valuable for those interested in understanding potential adjunct methods for managing periodontal diseases, but not limited to, dental professionals, clinical researchers and the public at large.

Keywords: periodontal disease, inflammation, inflammatory response, host modulation therapy, non-surgical therapy

OPEN ACCESS

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Specialty section:
This article was submitted to Periodontics, a section of the journal Frontiers in Dental Medicine

Received: *18 February 2022*
Accepted: *26 April 2022*
Published: *13 May 2022*

Citation:
Bezerra B, Monajemzadeh S, Silva D and Pirih FQ (2022) Modulating the Immune Response in Periodontitis. Front. Dent. Med. 3:879131. doi: 10.3389/fdmed.2022.879131

INTRODUCTION

Periodontal disease is a chronic inflammatory disease of the oral cavity with its primary etiological factor being bacterial plaque. In the US, almost half of the population presents with some form of periodontal disease (1). Management of periodontal disease consists of control of the bacterial biofilm, the primary etiological factor, however, the progression of the disease is highly dependent on the inflammatory response triggered by the bacterial plaque.

The host response to the supra- and subgingival biofilm accumulation can be a double-edge sword. It can be potentially protective, in which symbiosis between host-response and the biofilm is maintained, thus maintaining the tissue hemostasis where no periodontal tissue destruction is noted. Or it can be destructive, where a dysregulated immune response can assist in a shift in biofilm composition, giving way to growth of more pathogenic bacteria, which will continue to

activate the host immune response leading to a positive feedback loop of continued tissue destruction and maintenance of a dysbiotic microbial community (2). Studies have demonstrated a relationship between dysbiosis and inflammation, where inflammation fuels growth of dysbiotic communities and this dysbiosis exacerbates inflammation leading to destruction of periodontal tissues (3, 4).

Even though periodontitis is highly prevalent, its severity varies widely, and only a small proportion of the population presents with severe forms of the disease (1). This variation has been demonstrated by several studies (5, 6), however, it is still poorly understood why some individuals are more susceptible than others in developing periodontitis. Susceptibility has been proposed to be determined by several factors such as genetics, epigenetic, environmental, aging and systemic conditions which can modify the host immune response toward a protective or destructive pathway.

As a complex chronic inflammatory disease (7), periodontitis presents with a non-linear progression, where it has been demonstrated that the disease presents periods of remission, or stability, and progression (8, 9). These cycles between stability and progression are still poorly understood, as several factors could be simultaneously playing a role in dysregulating the host immune response. One thing is certain, the immune response is the main culprit for the tissue damage observed in periodontitis, and it is reasonable to propose host-modulating approaches for the management of periodontal disease as adjunct therapies for mechanical debridement.

In this review we will summarize the current concept of dysbiosis as it applies to the pathogenesis of periodontal disease, discuss potential mechanisms targeting modulation of the inflammatory response, and finally discuss advantages and drawbacks associated with host modulation therapy (HMT) for the management of periodontal disease.

PERIODONTAL DISEASE PATHOGENESIS AND THE ROLE OF THE HOST IMMUNE RESPONSE ON DYSBIOSIS

The role of bacteria as the primary etiological factor for periodontal disease was initially established by the classic study of Loe et al. (5) which confirmed that presence of plaque was necessary to elicit inflammatory changes to the gingival tissues in humans. Several studies followed which attempted to expose the role of specific bacteria in the progression of periodontal disease (10). As evidence accumulated, the role of the host immune response on the pathogenesis of periodontal disease has now extended beyond the model proposed by Page and Schroeder (11). Longitudinal studies have demonstrated that the presence of bacteria is necessary but not sufficient for development of periodontal disease, and support that a dysregulated immune response along with uncontrolled inflammation are responsible for the tissue destruction observed in periodontitis (12–14).

The polymicrobial synergy and dysbiosis theory (PSD) proposes that a synergistic polymicrobial community is responsible for initiating disease as several factors within this community lead to a dysregulation of the host inflammatory response (15). As disease progresses, the interactions between the polymicrobial community and the host immune response become a continuous cycle that perpetuates the dysbiosis leading to the tissue damage observed in periodontitis.

As bacterial biofilm accumulates in the supra and subgingival environment, the host responds with an inflammatory response aimed at maintaining homeostasis. If this inflammatory response is not properly resolved its persistence leads to the dysbiosis of the polymicrobial community. As a consequence of the dysbiotic community, a positive feedback loop is established where inflammatory tissue breakdown products serve as nutrients for the outgrowth of pathobionts (3, 16) and the dysbiotic microbial community continues to activate the immune response (4) leading to tissue damage. This self-sustained positive feedback loop is consistent with the chronic characteristic of periodontitis (**Figure 1**).

In vitro studies have shown that the availability of products derived from inflammatory tissue breakdown, such as amino acids, iron, etc., drives the outgrowth of pathogens which perpetuate the dysbiotic environment in the periodontal pocket (4, 15, 17). The inflammatory changes in the subgingival environment also have been known to elevate the expression of certain genes in subgingival bacteria that assist these pathobionts in exploiting these changes for their benefit (15, 18). Animal studies demonstrated that the inflammatory lesion observed in periodontitis contributes to the shift in the microbial community to one that is more gram-negative, anaerobic and proteolytic (19, 20).

As previously noted, the host response to the bacterial stimulus varies amongst individuals and this variation is due to a wide variety of determinants that play a role in the regulation of the immune response. A combination of genetic, environmental and lifestyle factors, and more recently, epigenetic factors, can affect an individual's susceptibility to and severity of periodontal disease (21, 22).

The site-specific presentation of periodontitis suggests that local factors could be playing a role in regulating genes associated with inflammation. The local factors present at the biofilm-gingival interface of the tooth could be driving the epigenetic modifications locally and resulting in an hyperinflammatory response (23). These modifications can not only be a direct result of bacteria and their products on epithelial cells, but also on inflammatory cells recruited to the area (24, 25). Currently, alterations in several genes involved in the inflammatory response in gingival tissue (23), peripheral blood and buccal mucosa (26–28) of periodontitis patients have been identified.

It is clear that a dysregulated inflammatory response is responsible for the tissue destruction observed in periodontitis. Current therapeutic methods for the management of periodontal disease focus mainly on the removal of bacterial plaque, however, it has been shown that this approach is not enough to halter the destruction of the periodontal tissues in some cases. With the current knowledge of the role of the inflammatory response on the destruction of these tissues, alternative methods targeting the immune response could provide clinicians with additional tools to manage periodontal disease.

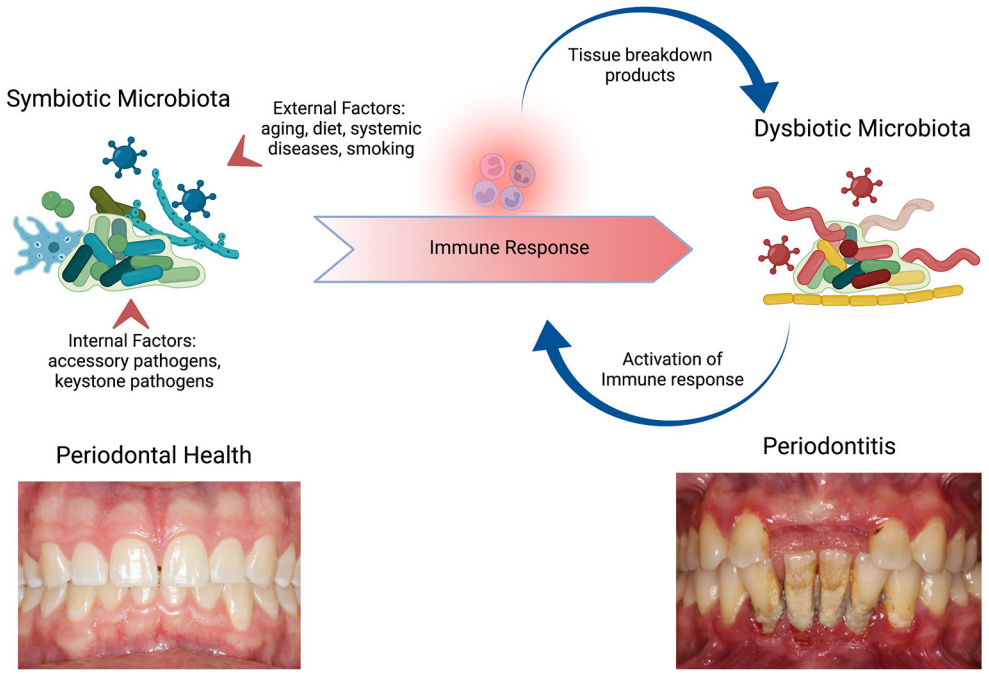

FIGURE 1 | Periodontal disease pathogenesis and the role of the immune response on dysbiosis. Periodontal health is maintained by a homeostasis between the symbiotic microbiota and the host immune response. The internal factors to the polymicrobial community, such as the colonization by keystone pathogens, and external factors, such as smoking, leads to alterations within the microbiota and the immune response to the new polymicrobial community, that is dysbiotic. The availability of nutrients (tissue breakdown products) promotes further growth of pathobionts leading to continuous activation of the immune response and consequently further tissue breakdown perpetuating the cycle. As a result, a self-sustaining loop is established and underlies the chronicity of periodontitis. *Adapted from "The Oral Microbiome," by BioRender.com (2022). Retrieved from https://app.Biorender.com/biorender-templates*.

HOST-MODULATION STRATEGIES IN THE MANAGEMENT OF PERIODONTITIS

The goal of HMT is to manipulate the immune response in order to prevent or ameliorate tissue damage, where hemostasis is achieved between the polymicrobial community and the host immune response. As we increase our understanding of the different inflammatory mechanisms involved in periodontal inflammation and tissue destruction, we can potentially identify therapeutic alternatives to be employed as adjuncts to mechanical debridement. On this review we will focus on therapies that present *in vivo* evidence, both animal and/or clinical studies, of improvement and/or prevention of periodontal tissue destruction. HTM strategies will be presented in a chronological order as we discuss the evolution of these strategies and their applications in the management of Periodontitis. A summary of these strategies can is available on **Table 1**.

Modulation of Arachidonic Acid Metabolites

Tissue damage caused by bacteria and/or the host immune response exposes phospholipids from plasma membranes which interact with phospholipase A2 promoting the release of arachidonic acid (AA). This cascade of events leads to the production of prostaglandins (PG) via the action of the cyclooxygenase enzyme (COX). Elevated levels of PGE2 have been identified in gingival crevicular fluid of patients with gingivitis, periodontitis and periimplantitis. PGE2 has even been reported to correlate with disease progression (75). The blockade of COX enzymes via use of NSAIDs has demonstrated the ability to inhibit bone resorption in both animal (33–36) and clinical studies (9, 37). The effects of these drugs, however, did not remain after withdrawal of the drug (29).

The use of both non-selective and selective COX inhibitors come with a range of side effects, as will any therapy that is provided systemically. With the current knowledge that this agent's benefits rapidly decline after stopping its use, its long-term use is not recommended due to its adverse effects. Adverse effects include damage to the gastrointestinal mucosa, renal toxicity and pro-thrombotic side effects (30–32).

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are proteolytic enzymes responsible for the breakdown of collagen. MMPs have been implicated in a variety of pathological conditions including periodontitis (76) and several resident and infiltrating cells within the extracellular matrix of the periodontium are able to secrete them. A balance between collagen breakdown and synthesis is achieved by endogenous tissue inhibitors of MMP (TIMPs) under healthy conditions (77). MMP-8 and MMP-9 are the predominant MMPs responsible for collagen breakdown in periodontitis, which are normally secreted by neutrophils

TABLE 1 | Host Modulation Therapy (HTM) agents in the treatment of periodontitis.

Category	Active agent	Mechanism of action	Advantages	Disadvantages	Status*
Arachidonic acid metabolites	Non-steroidal anti-inflammatory drugs (non-selective and selective COX inhibitors)	• Inhibition of COX, blocking PGE2 production		• Effects decline after drug withdrawal (29) • Several severe adverse effects (30–32)	• Animal studies (33–36) • Clinical studies (9, 37) *Not in use due to adverse effects
Matrix metalloproteinase inhibitors	1) Subantimicrobial dose Doxycycline (SDD)	• Inhibition of MMP-8	• No adverse side effects • Prolonged effect after drug withdrawal (up to 6 months) (38–44)	• Patient compliance	• Animal studies • Clinical studies (38–51) *FDA approved for use in treatment of periodontal disease (Periostat®)
	2) Chemically-modified tetracycline-3 (CMT-3)	• Inhibition of MMP-8 • Suppression of IL-1β	• No known adverse side effects	• Potential Patient compliance	• One pilot study available (52) • Studied application as cancer therapy (53, 54)
	3) Chemically-modified curcumin 2.24 (CMC 2.24)	• Inhibition MMP-8,9, 13 • Suppression of IL-1β, IL-6 and PGE2	• No known adverse side effects		• Animal studies only (55–57)
Cytokine inhibitors	TNF-α inhibitor IL-6 receptor antagonist	• Inhibition of pro-inflammatory cytokines via monoclonal antibodies or receptor antagonists	• May benefit patients with RA that present with periodontitis	• Single target, whereas tissue destruction is brought up by a network of cytokines • Potential adverse effects	• Clinical trials completed in patients with Rheumatoid Arthritis (58–62)
Lipid mediators of resolution of inflammation	Resolvin D-1, E-1 Lipoxin A4	• Resolution of inflammatory response *via* proresolving mediators	• Topical application (oral rinse) without systemic effects • No adverse effects reported (63)		• Animal studies (19, 20, 64–66) • Phase I Clinical trials (63)
Complement inhibitor	Cp40 (AMY-101)	• Inhibition of C3 component of the complement cascade • Reduction in levels of MMPs • Suppression of IL-17	• Prolonged effect after drug withdrawal (up to 6 weeks) • Local and systemic delivery with no to minimal side effects		• Animal studies (67–69) • Phase IIa Clinical Trials (70)
Epigenetic drugs	HDACi: Vorinostat, Romisdepsin DNMTi: Vidaza, Decitabine HMTi BETi	• Inhibition or activation of epigenetic proteins associated with disease	• N/A	• Limited information on role of epigenetics in periodontitis • Potential systemic adverse side effects	• *in vitro* and animal studies (71–74)

COX, cyclooxygenase enzyme; PGE2, prostaglandin E2; IL, interleukin; MMP, metalloproteinase; TNFα, Tumor necrosis factor alpha; RA, rheumatoid arthritis; HDACi, histone deacetylase inhibitors; DNMTi, DNA methyltransferase inhibitors; HMTi, histone methyltransferase inhibitors, BETi, bromodomain and extra-terminal domain protein inhibitors.

(45, 46), however, gingival fibroblasts, epithelial cells and monocyte/macrophages are also able to secrete them (78, 79).

The modulation of the host's collagenolytic response as an HMT targets the action of MMPs against the periodontium. As collagen is the most abundant component of the extracellular matrix in the periodontal tissues, targeting the mechanism responsible for collagen breakdown would be beneficial for managing periodontal tissue destruction.

Tetracyclines have demonstrated inhibitory activity against MMPs at low concentrations, called subantimicrobial doses (80). A series of *in vitro*, *in vivo,* and clinical studies have demonstrated effects of doxycycline in the inhibition of MMPs in gingival tissues and gingival crevicular fluid and concomitant improvements in periodontal status (45–47). Of the available tetracyclines, doxycycline has demonstrated to be more effective at inhibiting MMP-8, which is highly predominant in periodontitis (46, 81). Subantimicrobial dose doxycycline (SDD) has demonstrated no adverse side effects, including no impact on antibiotic resistance on either subgingival (48, 80) nor intestinal microbiota (82). The effect of SDD lies on the modulation of pathologic levels of MMPs which are secreted in excess as a result of the inflammatory process.

Clinical studies investigating the use of SDD as an adjunct to nonsurgical periodontal treatment have demonstrated that for benefits to be noted, at least a 3-month regimen is necessary (49). Among the clinically relevant benefits demonstrated by these

studies is an increased percentage of sites presenting probing depth reductions of 2 mm or more (50, 51). Long-term use of this HMT, treatments ranging from 3 months to 2 years, has shown to provide prolonged benefits, where studies have demonstrated the clinical benefits were maintained for at least 3 months after stopping treatment (38–43). Benefits were also noted when using SDD as an adjunct to periodontal surgery, where significant pocket depth reduction was achieved and maintained even after 6 months of discontinuing the medication (44).

As the only FDA-approved medication for the management of periodontitis, clinical studies have shown promising long-term effects on probing depth reduction and stability of clinical attachment loss. However, it is still not clear when to utilize it as an adjunct to periodontal treatment. Another aspect is patient compliance. As studies demonstrate that at least 3 months is required to see clinical benefits, patients must be committed to this regimen, including maintaining proper oral hygiene along with participating in maintenance recalls.

Most recently, chemically modified tetracyclines, which have been modified to eliminate the antibacterial activity of tetracycline while retaining the MMP inhibitory effects, have been developed. Chemically modified tetracycline-3 (CMT-3) showed major inhibitory activity against MMPs. Only one pilot clinical trial is available demonstrating the effects of low dose CMT-3 on periodontitis (52). This pilot study utilized 10mg of CMT-3 per day, instead of 50-100 mg per day as in previous cancer trials (53, 54). The authors observed a reduction in IL-1β and MMP-8 levels in the GCF of patients receiving scaling and root planing, when compared to placebo, with no adverse side effects.

Based on the limitations associated with tetracyclines, such as allergic reactions and adverse effects associated with pregnancy, the scope of use is limited. Recently, a novel compound derived from curcumin, has been developed at Stony Brook University, which has exhibited MMP inhibiting effects, including effects on MMP-9,−13, as well as suppressing inflammatory mediators IL-1β, IL-6 and PGE2 (55, 83). Chemically-modified curcumin-2.24 (CMC-2.24) has demonstrated anti-inflammatory effects as well as decreased bone loss in animal models of periodontal disease, with substantial impacts on IL-1β, MMP-9 and MMP-8 levels both locally (gingival tissues) and systemically (55–57). Currently no clinical trials are available testing the effects of CMC-2.24 as an adjunct for the treatment of periodontitis. Based on pre-clinical trials, the application of such molecules as HMT shows promises in the treatment and, potentially, prevention of periodontitis-induced bone loss.

Modulation of Cytokines

The activation of the immune response by the subgingival biofilm leads to the release of several pro-inflammatory cytokines which have been associated with the progression of periodontal bone loss. A several cytokines have been shown to play a role in the pathogenesis of periodontitis with its hallmark signs of bone loss and soft tissue destruction. These cytokines are secreted by different cells such as gingival epithelial cells, fibroblasts, endothelial cells, neutrophils among others present within the periodontal pocket environment.

The investigation on the use of anti-cytokine drugs for the management of periodontitis was by chance, as the goal of studies targeting the effects of these drugs was to investigate their efficacy on rheumatoid arthritis (RA) outcomes. Periodontitis and RA share similar inflammatory pathways, where overproduction of pro-inflammatory cytokines such as TNF-α and IL-6 have been implicated in the pathogenesis of both conditions (84). Some studies even suggesting a bidirectional link between these two chronic inflammatory conditions (85, 86). With such information is only natural to suggest that drugs currently used for the management of RA can potentially be used as an adjunctive therapy in the management of periodontal disease.

The investigation on the effects of anti-cytokine therapies on periodontal disease currently presents minimal evidence. The use of monoclonal antibodies, or receptor antagonists, to block the action of specific pro-inflammatory cytokines has been employed in the treatment of RA and findings on periodontal inflammation have been consequential as reported in the systematic review by Han and Reynolds (87).

More recently, an update on the topic provided by a systematic review and meta-analysis (88) investigating the influence of anti-rheumatic agents on the periodontal condition of RA patients with periodontitis demonstrated improvements in clinical parameters (bleeding on probing-BOP, probing depth-PD and clinical attachment levels-CAL) in patients who did not received periodontal treatment, and were treated with anti-IL-6R therapy (58, 59) and anti-TNF-α agents (60–62). This systematic review (88) points out that the studies included measured several periodontal parameters (PD, BOP, CAL) in patient with periodontitis, whereas the previous SR (87) included studies reporting only on BOP and GI, and RA patients with and without periodontitis.

Overall, the availability of clinical trials investigating the use of this drug class for the management of periodontal disease is low and this can be explained by the potential adverse effects that these drugs may pose to the patient's immune response, especially when being administered systematically. Among the adverse effects reported increased risk for serious bacterial, fungal and viral infections, drug-induced Lupus, lymphoma, just to list a few (89). Tissue destruction in periodontitis is the result of network of cytokines working in concert to activate different aspects of the immune response and blocking a single cytokine may not provide the expected effects ones is looking for.

Lipid Mediators of Resolution of Inflammation

Recent studies have demonstrated the presence of a pathway associated with the termination of acute inflammation (90, 91). Resolution of inflammation involves a sequence of events where pro-inflammatory mediators induce the production of specialized proresolving mediators, which in turn stimulate their receptor targets to inhibit different cells involved in the acute inflammatory response. This process seems to be initiated at the peak of the acute inflammatory response,

and if the resolution pathway fails to resolve inflammation, chronicity ensues.

Specialized proresolving mediators (SPM) are lipid mediators derived from dietary omega-3 polyunsaturated fatty-acids (resolvins, protectins) or endogenous fatty acids (lipoxins) (92). These mediators function as receptor agonists that initiate proresolving pathways and consequently promote the resolution of inflammation and return to homeostasis.

Resolvins can be divided into two major groups based on their chemical structures: E-series, which is derived from eicosapentaenoic acid (EPA), and D-series, derived from docosahexaenoic acid (DHA). E-series have demonstrated effects on neutrophils (93, 94), whereas D-series affects platelet-leukocyte adhesion and production of molecules with anti-inflammatory and proresolution functions (95). Overall, Resolvins activate the hallmark functions of resolution of inflammation by stopping neutrophil infiltration, activating neutrophil apoptosis, recruiting macrophages to phagocytose apoptotic neutrophils to clear the lesion thus enhancing clearance of inflammation in the lesion to promote tissue regeneration (19, 96, 97).

Investigation of the effects of SPM on periodontitis have shown a protective effect of these mediators on experimentally-induced periodontal bone loss as well as the ability to regenerate periodontal tissues (19, 20, 64–66). These studies investigated the effects of topically delivered SPM on experimental periodontitis with successful outcomes. These studies also demonstrated a shift in biofilm composition after treatment with Resolvin E-1 (RvE1), which the authors hypothesize to be a result of the proresolution effects of RvE1 *via* the release of antimicrobial peptides, reduced inflammatory mediators and increase bacterial clearance by macrophages, which promotes a change in the biofilm environment.

Clinical studies utilizing these molecules are scarce as they have not yet received approval for clinical use. There is, however, clinical data on the use of dietary supplementation with omega-3 PUFAs in combination with aspirin and its impact on treatment outcomes on periodontal disease. The addition of aspirin promotes the acetylation of and changes the enzymatic function of COX2 triggering the production of E- and D-resolvins, instead of prostaglandins (98). These studies have demonstrated beneficial effects when used as adjuncts to non-surgical periodontal treatment, showing significant improvements in probing depth reduction, gain in clinical attachment levels in both systemically healthy (99, 100) and Type 2 diabetic patients (101, 102).

The first clinical trial to investigate the effects of SPM on gingival inflammation (63) utilized a topical delivery method (oral rinse) to investigate the efficacy of Lipoxin A_4 mimetic ($BLXA_4$). This Phase 1 clinical trial demonstrated that once a day rinse with $BLXA_4$ was safe and well tolerated by the study participants, with no adverse effects. It also significantly reduced modified gingival index as compared to both placebo and no rinse group. Data also showed a steady and more pronounced reduction in bleeding on probing, probing depth and gain in clinical attachment, however these results were not significant.

The application of SPM as an HMT is an evolving field with promising effects on controlling periodontal tissue destruction and potentially leading to regeneration of lost tissues. As studies continue to dissect the mechanisms involved in resolution of inflammation via use of SPMs, this appears to be the most promising therapy as it has demonstrated thus far no adverse side effects with its application.

Complement Inhibitors

The complement system is responsible for regulating immunity and inflammation and it comprises of a network of over 50 proteins (103, 104). The activation of the complement system can follow three distinct pathways, however all three converge to the central complement component C3. C3 has been linked to periodontitis, where elevated levels have been noted in an experimental gingivitis study in humans (105) and successful periodontal treatment resulted in decreased C3 activation in gingival crevicular fluid (GCF) (106) and saliva (107). Animal studies also demonstrated that mice deficient in C3 did not exhibit periodontal bone loss in an experimental periodontitis model (108, 109).

Data from preclinical studies indicate that targeting the complement cascade could be a novel method for controlling the immune response in periodontitis and thus preventing tissue destruction. Different antagonists have been studied and demonstrated inhibition of alveolar bone loss as well as suppression of pro-inflammatory cytokines (67, 110, 111). A novel complement inhibitor targeting C3 (Cp40) has demonstrated inhibition of inflammation and bone loss in a non-human primate model of periodontitis when applied intragingivally (109). Other effects included inhibition of naturally occurring periodontitis in aging non-human primates even in the absence of periodontal treatment (68, 69), with effects of drug still present 6 weeks after session of treatment. The observed effects of inhibiting C3 component occurs via suppression of T-helper 17 cells. By blocking the action of the complement in activating Th17 cells, secretion of IL-17 is blocked and MMPs and TNF ligand superfamily cannot promote degradation of connective tissues and alveolar bone (112).

Safety concerns have been raised with this therapeutic application, as the complement system plays a role in antimicrobial defenses, which may increase the risk of infections. The studies evaluating systemic treatment with Cp40 demonstrated no significant differences in biochemical, immunological, and hematological parameters in blood or tissues when compared to vehicle alone (113). Intragingival application of the Cp40 result in no local irritation (68). Recently, the safety of this drug was tested in healthy volunteers and was demonstrated to be safe and well tolerated (114).

Current results of a Phase IIa clinical trial utilizing Cp40 for the treatment of periodontal inflammation (70) demonstrated that local delivery of Cp40, *via* intragingival injections, significantly reduced gingival inflammation with

effects lasting at least 3 months after initial treatment. The authors noted that this improvement was mainly due to the host-modulating effect of the drug rather than a reduction in the amount of accumulated plaque. Treatment also led to a significant reduction in MMP-8 and−9 levels in the gingival crevicular fluid, which are key proteases associated with periodontal tissue destruction. Unfortunately, this trial was not able to assess the effects of the drug on periodontitis, as most of the patients included presented gingivitis.

Thus far, the safety and efficacy of the local application of Cp40 suggest that this could be a promising HMT for the treatment of periodontitis. Further studies are warranted to investigate its therapeutic effects on periodontitis and any potential systemic effects with its long-term application.

Epigenetic Drugs

As previously discussed, environmental and lifestyle factors, such as aging, systemic diseases and smoking, can induce epigenetic changes, modifying the DNA structure, which can contribute to the expression of genes associated with a hyperinflammatory state. DNA methylation and posttranslational modifications (PTMs) of histones have been implicated in alterations of the immune response (115) and demonstrated in gingival samples obtained from patients with periodontitis (26, 116–118).

Epigenetic drugs, or epidrugs, are drugs that target epigenetic markers responsible for the epigenetic alterations leading to inhibition or activation of disease-associated epigenetic proteins leading to improvement, cure, or prevention of the disease (119). These drugs have been widely studied in the treatment of cancer and information has emerged of their anti-inflammatory properties (71). Data from *in vitro* and animal studies have thus far demonstrated effects on suppression of alveolar bone loss (72), inhibition of pro-inflammatory cytokine production (73), and enhanced osteogenic differentiation (74).

These drugs target DNA methylation, histone acetylation and methylation, among other proteins associated with transcription-related processes. Some of them include histone deacetylase inhibitors (HDACi), histone methyltransferase inhibitors (HMTi), DNA methyltransferase inhibitors (DNMTi), bromodomain and extra-terminal domain protein inhibitors (BETi). Currently several epidrugs have received FDA approval for cancer therapy, including HDACis Vorinostat and Romidepsin, as well as DNMTis Vidaza and Decitabine, while several others are at pre-clinical and clinical trial phases (120).

The field of epigenetics in Periodontitis is expanding but very limited information on the role of epigenetic modifications on the pathogenesis of periodontal disease is available. As more studies become available and help elucidate the role of specific epigenetic modifications in the pathogenesis of periodontitis, we will be better equipped to apply the knowledge obtained from the use of epidrugs as an adjunct therapy in periodontitis.

CONCLUSIONS

As our knowledge of the pathogenesis of periodontitis increases, with a better understanding that the host immune response is the main culprit for the tissue destruction observed with periodontal disease, as well as its role in the dysbiosis of the microbial community, we are drawn to consider alternative methods to aid in the treatment of periodontitis. Understanding the different inflammatory mechanisms responsible for both soft and hard tissue destruction associated with periodontal disease allows us to target these processes implicated in tissue destruction. However, when modulating the host immune response, one must keep in mind that a single target may not be sufficient to halt the inflammatory events associated with periodontal attachment loss.

In this review we have discussed the available evidence regarding different methods of host modulation. Due to the chronicity of periodontitis, use of these medications many times need to occur for long periods of time for them to provide any clinical benefits, and this may lead to unwanted and, sometimes, serious adverse effects. HMT may be of particular interest for those patients who are at greater risk for experiencing attachment loss, such as patients with diabetes, smokers, or who do not respond well to non-surgical therapy.

Some of the available HMTs have demonstrated not only an impact on the inflammatory response, but also on the microbial community associated with periodontitis. By resolving inflammation, the dysbiotic community that was previously established returned to homeostatic conditions. These findings suggest that HMTs can also potentially be used to prevent periodontal disease, especially in high-risk populations. Future clinical studies investigating the effects of these drugs should not only address the clinical benefits as it reflects on reduced BOP, PD, and CAL, but also the long-term effects these drugs may possess, as the chronic nature of periodontal disease must be kept in mind. Delivery methods should also be investigated, as systemically administered drugs can potentially result in more adverse effects compared to local delivery.

AUTHOR CONTRIBUTIONS

BB and FP contributed to the conceptualization of the manuscript and revision of the manuscript. BB, SM, and DS contributed to literature review and writing of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdmed.2022.879131/full#supplementary-material

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