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C3 TARGETED THERAPY IN PERIODONTOLOGY: A REVIEW

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ABSTRACT

Periodontitis is a chronic inflammatory disease characterized by dysbiotic biofilms and a dysregulated host immune response that drives progressive destruction of periodontal supporting tissues. Conventional mechanical and antimicrobial therapies primarily target bacterial burden but often fail to achieve long-term disease control due to persistent host-mediated inflammation. Increasing evidence highlights the complement system, particularly complement component C3, as a central regulator of periodontal inflammation and bone loss. Dysregulated C3 activation amplifies inflammatory signaling through generation of C3a and C5a, promotes osteoclastogenesis, and sustains tissue destruction via crosstalk with Toll-like receptors. C3-targeted therapies, especially peptide-based inhibitors such as compstatin analogs and AMY-101, have demonstrated significant anti-inflammatory and bone-protective effects in experimental models and early-phase clinical trials. These agents offer a novel host-modulatory approach that suppresses pathogenic inflammation while preserving essential immune functions. This review summarizes the role of C3 in periodontal pathogenesis, evaluates current evidence on C3 inhibition, and discusses future perspectives for precision-based periodontal and peri-implant therapy.

KEYWORDS: *Periodontitis; Complement C3; Host modulation therapy; AMY-101; Periodontal inflammation*

INTRODUCTION

Periodontitis is widely acknowledged as a chronic, multifactorial inflammatory disorder initiated by dysbiotic dental biofilms and perpetuated by an exaggerated and poorly regulated host immune response, ultimately resulting in the progressive destruction of the periodontal ligament and alveolar bone.[1] Although conventional periodontal therapy primarily aims to reduce microbial burden through mechanical debridement and adjunctive antimicrobials, long-term disease stability is often difficult to achieve because tissue damage is largely mediated by sustained host-driven inflammation rather than the mere presence of bacteria.[2]

The pathogenesis of periodontitis involves complex interactions between innate and adaptive immune mechanisms, with pro-inflammatory cytokines such as interleukin-1β, interleukin-6, interleukin-17, and tumor necrosis factor-α playing central roles in connective tissue degradation and osteoclast-mediated bone resorption, while keystone pathogens, notably *Porphyromonas gingivalis*, manipulate host immunity to promote microbial dysbiosis and amplify destructive inflammatory signaling. [3]Although scaling and root planing, with or without adjunctive antibiotics, can produce short-term improvements in probing depth and clinical attachment levels, their benefits are often transient and accompanied by concerns related to antimicrobial resistance, adverse effects, and incomplete eradication of pathogens residing within complex biofilms or invading periodontal tissues; consequently, current guidelines limit the routine use of systemic antibiotics, particularly in mild to moderate disease.[4]

These limitations have driven a paradigm shift toward host modulation therapy, which seeks to attenuate excessive inflammatory responses and enhance resolution pathways using agents such as sub-antimicrobial dose doxycycline and emerging biologics, thereby addressing the underlying immunopathology responsible for unpredictable treatment outcomes in susceptible individuals.[5] Within this context, the complement system has gained increasing attention, as it represents a key interface between microbial challenge and host inflammation; activation through the classical, lectin, or alternative pathways converges at complement component C3, whose cleavage into C3a and C3b mediates anaphylatoxin signaling, opsonization, and amplification of Toll-like receptor–driven inflammatory cascades. In periodontitis, excessive local complement activation has been shown to correlate with disease severity, a process further intensified by periodontal pathogens that impair complement regulatory mechanisms.[6]

The complement component C3 occupies a pivotal position in the complement cascade, and its dysregulated activation has been strongly implicated in sustaining periodontal inflammation and driving connective tissue breakdown and alveolar bone loss, as highlighted by Hajishengallis et al. (2020).[6] Therapeutic inhibition of C3, particularly using agents such as AMY-101, has demonstrated the ability to dampen excessive inflammatory responses, restore immune balance, and improve periodontal clinical parameters, with supportive evidence from both experimental and clinical investigations (Agnihotri et al , 2022).[7]

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Notably, a Phase IIa clinical trial reported by Alayash et al. (2023)[8] showed that local administration of AMY-101 resulted in a significant reduction in gingival inflammation and probing pocket depth in patients with chronic periodontitis, underscoring its translational potential. Complementary animal studies further revealed that C3 inhibition was associated with reduced expression of pro-inflammatory cytokines, suppression of osteoclastogenic activity, and overall improvement in periodontal indices, reinforcing the biological plausibility of this therapeutic strategy (Agnihotri, 2022; Chen et al., 2024).[7,9] Looking ahead, ongoing research is directed toward establishing the long-term efficacy and safety profile of C3 inhibitors through larger, well-designed clinical trials, as well as identifying genetic and molecular factors that may influence individual treatment responses (Alayash et al., 2023).[8] In addition, emerging approaches such as siRNA-based therapies targeting C3 have shown encouraging results in experimental models by attenuating inflammatory signaling and bone resorption, thereby opening new avenues for precision-based periodontal therapy (Chen et al., 2024).[9]

Complement System in Periodontal Health and Disease

Periodontitis is characterized by dysregulated activation of the complement system, wherein protective innate immune mechanisms become exaggerated and perpetuate destructive inflammation. Complement activation is initiated through three interconnected pathways that all converge at complement component C3.[5] The classical pathway is triggered by the binding of C1q to antibody–antigen complexes or acute-phase proteins such as pentraxins, leading to activation of C1r and C1s and subsequent cleavage of C4 and C2 to form the C3 convertase C4b2a. Similarly, the lectin pathway is initiated when pattern-recognition molecules, including mannose-binding lectin and ficolins, recognize microbial carbohydrate structures and associate with mannose-binding lectin–associated serine proteases (MASP-1 and MASP-2), resulting in the formation of the same C3 convertase. In contrast, the alternative pathway is constitutively active at low levels through spontaneous hydrolysis of C3 to C3(H_2O) and is rapidly amplified on microbial surfaces that lack appropriate regulatory proteins via the actions of factors B and D.[6]

Activation of C3 represents the central amplification step of the complement cascade, generating the anaphylatoxin C3a and the opsonin C3b, while downstream cleavage of C5 produces the potent inflammatory mediator C5a and initiates assembly of the membrane attack complex (C5b–9). Under physiological conditions, complement plays a crucial role in oral immune surveillance by facilitating opsonization and phagocytic clearance of periodontal pathogens such as *Porphyromonas gingivalis*, promoting microbial lysis through membrane attack complex formation, and aiding in the removal of immune complexes and apoptotic neutrophils from the gingival crevicular environment, thereby supporting timely resolution of inflammation.[10] However, in periodontitis, this tightly regulated system becomes subverted by pathogenic bacteria that impair complement regulatory mechanisms, for instance through the proteolytic activity of gingipains that degrade complement components and regulators, resulting in excessive local generation of C3a and C5a.[11]

These complement-derived mediators engage in synergistic crosstalk with Toll-like receptors on gingival fibroblasts, immune cells, and osteoclast precursors, markedly enhancing the production of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α, as well as upregulating receptor activator of nuclear factor kappa-B ligand (RANKL). This amplified inflammatory signaling promotes osteoclastogenesis, alveolar bone resorption, and the persistence of chronic inflammation, thereby sustaining periodontal tissue destruction even after conventional mechanical debridement.[12]

Central Role of Complement Component C3 in Periodontal Tissue Destruction

Complement component C3 functions as the pivotal molecular hub in complement-driven periodontal pathology, integrating signals from all activation pathways and orchestrating inflammatory and tissue-destructive processes. The classical, lectin, and alternative complement pathways all converge at C3, where pathway-specific C3 convertases cleave it into the biologically active fragments C3a and C3b. While C3a acts as a potent pro-inflammatory anaphylatoxin, C3b serves as a key opsonin and drives further complement activation through the alternative pathway amplification loop, which is initiated by spontaneous C3 hydrolysis and preferentially stabilized on microbial surfaces.[13]

This amplification mechanism accounts for the majority of C3b generation contributing to more than 80% of overall complement activity and plays a dominant role in sustaining excessive complement activation in periodontitis. Elevated levels of C3 and its activation products have been consistently detected in gingival crevicular fluid and periodontal tissues of affected individuals, with concentrations closely correlating with clinical indicators of disease severity.[14]

Functionally, C3a promotes the recruitment and hyperactivation of neutrophils via C3a receptor signaling, leading to exaggerated neutrophil extracellular trap formation and the release of tissue-damaging proteases that intensify gingival inflammation. In parallel, C3-driven signaling enhances osteoclastogenesis by upregulating receptor activator of nuclear factor kappa-B ligand expression on gingival fibroblasts and osteoblast-lineage cells, while synergistic interactions between complement receptors and Toll-like receptors amplify the production of pro-inflammatory cytokines, including interleukin-1β, tumor necrosis factor-α, and interleukin-6, thereby accelerating alveolar bone resorption.[15]

From a therapeutic standpoint, targeting C3 offers distinct advantages, as upstream inhibition effectively intercepts all complement pathways and their amplification loops, providing broader control of pathogenic inflammation compared with selective upstream or downstream targets. In contrast to strategies that focus solely on C5a or membrane attack complex inhibition which fail to address the critical role of C3a-mediated inflammation C3 inhibition suppresses both major inflammatory effectors while maintaining essential opsonophagocytic functions.[16] Moreover, localized delivery approaches, such as subgingival administration of C3 inhibitors

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like AMY-101, enable high drug concentrations at diseased sites with minimal systemic exposure, thereby reducing the risk of generalized immunosuppression while effectively attenuating complement-mediated periodontal tissue destruction.[17]

Table: C3-Targeted Therapeutic Agents in Periodontology

Therapeutic Agent / Class	Mechanism of Action	Key Properties	Evidence in Periodontology
Compstatin (Parent peptide)	Cyclic 13–amino-acid peptide that binds native C3 and sterically blocks C3 convertase–mediated cleavage	Moderate affinity (Kd ≈ 1 μM); primate-specific; minimal off-target effects	Proof-of-concept studies demonstrating inhibition of complement activation
Compstatin analogs	Enhanced C3 binding prevents generation of C3a and C3b and halts amplification loop	100–500× higher potency than parent compound; improved protease resistance and solubility	Extensive preclinical validation
AMY-101 (Cp40)	High-affinity C3 inhibitor preventing downstream C3a/C5a generation and MAC formation	Prolonged gingival retention (up to 6 weeks); micromolar tissue concentrations	NHP models: reduced pocket depth, gingival inflammation, bone loss, TNF-α, IL-1β; Phase IIa trial: ↓ gingival index (~33%), ↓ MMP-8/9 at 3 months as SRP adjunct
Small-molecule C3 modulators (e.g., KPL-404)	Inhibit C3 convertase activity via non-peptide mechanisms	Oral bioavailability; systemic administration possible	Currently limited to preclinical or non-periodontal studies
Nanoparticle-based C3 delivery systems	Encapsulation of compstatin analogs for controlled local release	Site-specific delivery; prolonged retention in periodontal pockets	Preclinical experimental models
Hydrogel-based C3 inhibitor formulations	Sustained release of C3 inhibitors at diseased sites	Injectable, biodegradable, pocket-retentive	Early experimental studies

Future Perspectives of C3-Targeted Therapy in Periodontal and Peri-Implant Care

C3-targeted therapeutic strategies possess the potential to fundamentally reshape periodontal care by advancing treatment paradigms from uniform adjunctive approaches toward precision-based, patient-centered management. Emerging evidence suggests that genetic profiling of complement-related polymorphisms, particularly variants affecting C3 regulation, together with the assessment of local biomarkers such as C3a concentrations in gingival crevicular fluid, could enable identification of individuals at heightened risk for aggressive or treatment-refractory periodontitis, thereby allowing selective and optimized use of complement inhibition. In parallel, the development of chairside diagnostic platforms capable of real-time quantification of C3 activation fragments in gingival crevicular fluid may facilitate dynamic monitoring of inflammatory activity, enabling clinicians to tailor dosing, frequency, and duration of therapy based on biological response rather than empirical protocols.[18]

Beyond inflammation control, integration of C3 inhibitors with regenerative modalities such as enamel matrix derivatives, bone grafts, or growth factor-based therapies following mechanical debridement may create a more favorable wound-healing microenvironment by suppressing excessive inflammation during guided tissue regeneration, ultimately enhancing new attachment formation in intrabony periodontal defects.[19] The relevance of C3 modulation also extends to peri-implant diseases, as peri-implantitis shares similar dysbiosis-driven complement dysregulation; localized delivery of C3 inhibitors such as AMY-101 around compromised implants holds promise for limiting peri-implant bone loss and improving inflammation and systemic conditions including atherosclerosis and rheumatoid arthritis, targeted suppression of pathological C3 activation within the periodontal milieu may confer broader systemic benefits, positioning the oral cavity as an accessible and strategically advantageous site for modulating complement-driven inflammatory comorbidities.[20]

DISCUSSION

C3-targeted therapy represents a significant advancement in host modulation strategies for periodontitis by directly intervening in complement-driven inflammation. Evidence from preclinical and early clinical studies indicates that inhibition of C3 effectively reduces pro-inflammatory cytokine production, osteoclast activation, and alveolar bone loss.[16] Unlike conventional antimicrobial approaches, C3 inhibition addresses the underlying immune dysregulation that sustains tissue destruction. Agents such as AMY-101 have demonstrated sustained local effects with minimal systemic exposure, enhancing their therapeutic appeal. The ability to block all complement pathways at a central convergence point offers broader control compared to downstream targets alone.[19] However, long-term safety and the impact on protective host

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defense mechanisms require further evaluation. Standardization of dosing protocols and patient selection criteria will be critical for clinical translation. Overall, C3 modulation holds promise as a precision-based adjunct in modern periodontal therapy.[20]

CONCLUSION

Complement component C3 has emerged as a highly promising therapeutic target in periodontology due to its central role in driving dysregulated inflammation and periodontal tissue destruction. Targeting C3 offers strong translational potential, supported by robust preclinical evidence and encouraging early-phase clinical trial outcomes. However, larger, well-designed randomized controlled trials are essential to establish long-term efficacy, safety, and clinical applicability. Overall, C3-targeted therapy represents a paradigm shift from traditional bacteria-centric approaches toward immune-centric, precision-based management of periodontal disease.

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