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Targeting the Complement System in the Management of Periodontal Disease

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Abstract

Periodontitis is a chronic inflammatory disease triggered by microbial antigens colonizing the root surface and pocket epithelium. While mechanotherapy aimed at debridement of root surface biofilms remains the primary treatment, adjunctive therapies targeting host immune responses have gained attention in recent years. The complement system, a key component of innate immunity, plays a crucial role in the pathogenesis of periodontal disease by amplifying inflammatory responses and modulating immune cell activity.

Keywords: Complement system, Host response, Periodontitis

1. Introduction

Periodontitis is a result of a chronic non-resolving inflammation that is evoked in response to microbial antigens colonizing the root surface and pocket epithelium.(1) Mechanotherapy that is largely directed towards the debridement of root surface biofilms continues to be the mainstay in the management of periodontal diseases.(2) However, in recent years, adjunctive measures such as modulating the host response have gained considerable attention albeit not always with predictable results.(3)

As periodontal disease is thought to result from the entire subgingival microbial community rather than individual pathogens, the innate immune responses are thought to be more appropriate for such host immunomodulatory therapies.(3) The complement system, consisting of a network of plasma proteins and cell surface receptors, plays a crucial part in coordinating the innate immune mechanisms in periodontal disease.(4) This mini-review highlights the recent advances made in regulating the complement cascade in the treatment of periodontal disease.

2. Complement System and its Role in Pathogenesis of Periodontal Disease

The Complement system plays a crucial role in the innate immune mechanisms through direct effects or via cross-talk and regulation of other host signaling pathways. The complement system comprises of some 50 proteins, including the classic serum proteins C1-9, pattern-recognition and regulatory molecules that interact with a variety of immune mediators.(5) The complement cascade, that is initiated by three distinct mechanisms (i.e. The classical, lectin, or alternative pathways), converge at the third complement component – C3.(6) C3a and C5a fragments released during the activation cascade are powerful anaphylatoxins that have significant immunomodulatory and pro-inflammatory effects.(7)

Along with their release, they activate certain G-protein coupled receptors C3aR and C5aR respectively and mediate mobilization and activation of leukocytes.(4). Immune system subversion/dysregulation that is associated with the dysbiotic biofilm has been an integral part of the pathogenic process in periodontal disease. The complement system, with its ability to not only affect inflammatory responses but also regulate other immune cells, is thought to play a greater role in mediating the disease process than previously realized.(4)

Fragments of complement products are either absent or present in low concentrations in periodontally healthy individuals. However, they are abundant in both GCF and serum of patients with periodontitis.(8) C3aR or C5aR signaling pathways cross-talk with and amplify TLR-dependent inflammatory responses in both the circulation and peripheral tissues including the periodontium.(4) This cross-talk has been documented to increase the inflammatory responses while at the same time suppressing the microbial clearance. Specifically, Porphyromonas Gingivalis subverts C5a receptor (C5aR; CD88) and impairs host defense mechanisms leading to the development of a dysbiotic microbiota that thrives in an inflammophilic environment.(9)

It, therefore, seems reasonable that periodontal disease could be prevented or mitigated by interventions aimed at regulating the complement cascade thereby controlling inflammation and counteracting microbial subversion of the host response(10).The complement cascade has been targeted at C3, C5aR levels.

3. AMY-101

Compstatin analogs which binds to the complement protein C3, prevents its cleavage by C3 convertases thereby preventing downstream activation of the cascade.(4) Cp40, a third-generation compstatin analog of cyclic peptidic inhibitors was clinically developed as AMY-101.(11)

The suitability of AMY101 in periodontitis, first tested in NHPs, has progressed to Phase1 human trials where clinically significant results were reported in relation to indices that measured gingival inflammation without any changes in PD and CAL (Mastellos ,2019) (Hasturk, 2021) (Tonetti, 2018)(11) . It is noteworthy that this improvement was reported even in the absence of additional mechanotherapy.(4)

4. PMX-53

PMX-53, a C5aR antagonist, blocked periodontal inflammation and bone loss in a mouse model of periodontitis, regardless of whether it was administered before or after disease initiation (Wang, 2010, Liang, 2011)(12). Local administration of PMX-53 was reported to result in almost complete elimination of the keystone P. Gingivalis, accompanied by a more than 10 fold reduction in the total numbers of oral anaerobic bacteria (Hajishengallis, 2011). (9)

5. CONCLUSION

Existing periodontal treatment modalities do not address the issue of individual disease susceptibility or recurrence and therefore fail to achieve the envisioned goal of precision periodontics. Complement inhibitors such as AMY101 and PMX53 could be used as chemotherapeutic agents that may regulate the inflammatory responses in susceptible patients. The efficacy and safety profile of these chemotherapeutic agents need to be tested in Phase 2 & 3 clinical trials before widespread clinical use.

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